

The Pholcodine Story

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KEYWORDS

- Anaphylaxis • IgE antibodies • Neuromuscular blocking agents
- Pholcodine • Suxamethonium

Adverse reactions during general anesthesia in the form of anaphylaxis have been reported with increasing frequency during the past decades.¹ Although still rare in absolute numbers, they constitute a mounting threat to patient safety and a challenge to the diagnostic and therapeutic skills of anesthetists. Even when appropriately treated, mortality rates between 3.5% and 10% are reported.^{2–4} Neuromuscular blocking agents (NMBAs) represent the most frequent cause, with suxamethonium (SUX) as the prominent culprit drug.

In most cases, the reactions appear IgE-mediated. Studies back in the 1980s identified the quaternary ammonium ion (QAI) as the most likely allergenic epitope for the specific binding of IgE to the NMBA.⁵ Since up to half of the patients with NMBA-related anaphylactic reactions have not previously been exposed to anesthetic drugs,¹ IgE sensitization must have been initiated by some of the many other drugs such as morphine (MOR) derivatives or environmental chemicals known to contain the QAI epitope.

To screen for individuals IgE-sensitized to the QAI epitope, MOR has been suggested.⁶ MOR has an unusual alkaloid structure with only one QAI epitope, which actually is a tertiary amine (**Fig. 1**). Therefore, it cannot by itself trigger mast cells or basophiles sensitized with IgE antibodies to QAI, but has been suggested for the detection of an IgE-sensitization to NMBA.

ANAPHYLAXIS TO NEUROMUSCULAR BLOCKING AGENTS IN NORWAY

During the 1990s, growing concern over the apparently increasing challenge of anaphylactic reactions during general anesthesia was voiced from anesthesiologists

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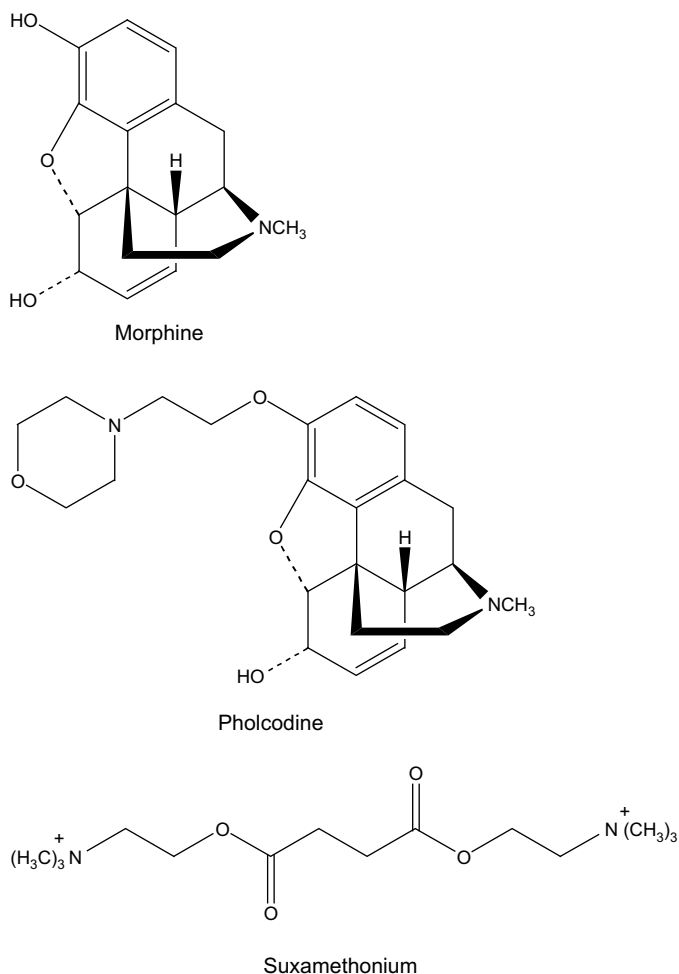


Fig. 1. The structures of MOR, PHO, and SUX. (From Florvaag E, Johansson SGO, Öman H, et al. Prevalence of IgE antibodies to morphine. Relation to the high and low incidence of NMBA anaphylaxis in Norway and Sweden, respectively. *Acta Anaesthesiol Scand* 2005;49:442; with permission.)

and the Norwegian Medicines Agency.⁷ Some key issues were the uncertainties in estimating prevalences and calculating the anaphylactic risk of individual NMBAs relative to their market shares. Several of the controversies were related to the statistical challenge posed by the rarity of reactions and the drawbacks of the spontaneous reporting systems on which the official strategies were based. In addition, criticism was pointed at the validity of the diagnostic methods applied in follow-up examinations. In a cooperation between anesthesiologists and allergy-competent specialists (allergology is not a medical specialty in Norway), the Norwegian Network for Anaphylactic Reactions during Anaesthesia (NARA) was started in 1998. It established and better standardized national routines for immediate and follow-up diagnostic investigations.

Based on a standardized follow-up protocol and 83 cases of anaphylaxis during anesthesia referred to the Section for Clinical Allergology, Department of Occupational Medicine, Bergen, Norway during a 6-year period, the first Norwegian clinical report

was published.⁸ An in-hospital frequency of one anaphylactic reaction per 5,200 general anesthetics, where NMBAs were administered, was found. Further, 71.1% of the reactions were classified as IgE-mediated, of which 93.2% were related to NMBAs, primarily SUX and rocuronium. Only 3.6% were caused by latex and the few remaining cases by other exposures. It could also be very carefully estimated from the in-hospital data that if, at the time of a SUX-induced anesthesia, a patient was IgE-sensitized to SUX, the risk of anaphylaxis would be around 1:20.⁹

THE COMPARATIVE RESEARCH MODEL FOR THE DIFFERENCES BETWEEN NORWAY AND SWEDEN

The prevalence data for Norway based partly on official spontaneous reports and partly on the 6-year single center study showed that anaphylactic reactions to NMBAs were on the order of 10 times higher in Norway than in Sweden. Such differences between these nations could have a number of reasons. One clearly had to consider the biases inherent in spontaneous reporting systems, different anesthetic practices, and the fact that in Norway a specialized diagnostic service was established through NARA. Finally, one had to consider the possibility that the two populations were differently exposed to an unknown environmental factor that gave rise to production of IgE-antibodies with specificities relevant for the QAI-epitope.

To our surprise, while establishing a radioimmunoassay for morphine at our laboratory we observed that in a control group of allergic subjects with serum IgE-levels of 1,000 kU/L or more about 30% had IgE-antibodies to MOR. The bindings were completely inhibited by MOR, indicating that they were immunologic and epitope specific and not caused by any unspecific mechanism. The data (unpublished) naturally gave rise to the somewhat intriguing question of why so many allergic Norwegians were IgE-sensitized to MOR. At that time, the best answer we could come up with was that it probably had to do with exposure to an unknown environmental factor.

Against this background, we decided to use the socially and geographically closely related countries Norway and Sweden as a research model. The authors considered that the genetics would be similar and knew that the anesthetic practices were largely identical. Studies were primarily set up to look for any significant differences in exposure to QAI-containing substances between the two countries and, if such a difference was identified, whether it would give rise to differences in IgE-sensitization.

ENVIRONMENTAL EXPOSURE STUDIES

To look for the proposed unknown exposure factor, 84 household and other environmental chemicals (skin care ointments, hair care products, cough syrups, lozenges, toothpastes, cleansers, and motor oils) were collected from the homes of both MOR- and SUX-sensitized and nonsensitized individuals in Bergen and Stockholm. Several of these chemical products inhibited IgE binding to SUX and MOR, thus confirming a sensitizing potential. However, Swedes and Norwegians seemed to be equally exposed to the same household chemicals and no definite differences in exposures was found.

Examining the other main group of exposures to the QAI structure, namely drugs, the populations in the two countries, although to different degrees, were exposed to the same compounds. However, there was one decisive exception: the use in Norway, but not in Sweden, of a cough mixture that, in contrast to all other drugs, contained pholcodine (PHO).

To explore this intriguing discrepancy in exposure, the authors decided to perform a comparative study with the aim of documenting the prevalence of IgE-sensitization

to PHO in comparative populations in Norway and Sweden. Sera from allergic patients with known or suspected IgE-mediated airway or skin allergy, and healthy controls (blood donors), were tested for IgE antibodies to PHO, MOR, and SUX using ImmunoCAP (Phadia AB, Uppsala, Sweden), and compared to sera from patients with a documented IgE-mediated, NMBA-initiated anaphylactic reaction.

Serum samples were obtained from the allergy diagnostic laboratories at Haukeland University Hospital, Bergen, Norway, and Karolinska University Hospital, Stockholm, Sweden. Three hundred samples from each laboratory were collected consecutively during the period from March to April 2002, from volumes left after analyses for IgE antibodies requested by referring physicians. In addition, serum samples from 500 and 1000 blood donors in Bergen and Stockholm, respectively, were included. For comparison, serum samples from 65 Norwegian patients with a documented IgE-mediated, NMBA-induced anaphylactic reaction during anesthesia were analyzed.

The results showed that in Norway 0.4% of blood donors, 3.7% of allergic patients, and 38.5% of patients with anaphylactic reaction to NMBAs were sensitized to SUX; as were 5%, 10%, and 66.7%, respectively, to MOR.¹⁰ Among blood donors and allergic patients from Stockholm, none with IgE antibodies to SUX or MOR was found. IgE antibodies to PHO, were found in 6% of blood donors from Bergen, but in none from Stockholm.

Thus, since more than 10 times as many blood donors and 3 times as many allergic patients had IgE antibodies to MOR than to SUX, the former is not ideal for screening of sera for IgE-sensitization to QAI in a country like Norway.

THE PHOLCODINE HYPOTHESIS

Pholcodine (3-(2-morpholinoethyl)morphine) was originally synthesized in France in the 1950s. In principle, it is a morphine molecule with a morpholino side chain (see **Fig. 1**). This modification changes its pharmacological effects in that it does not cause depression of respiration, pain relief, and central nervous system (CNS) excitation, and thus is void of euphorizing properties and risk of addiction. PHO is a cough suppressant acting directly on the cough center of the CNS, and has become a widely used cough medicine in numerous formulations. After single doses, it is rapidly absorbed from the gastrointestinal tract ($t_{\max} = 1.6 \pm 1.2$ h), but eliminated much more slowly than other opiates with a mean half-life of 50.1 ± 4.1 h. It freely crosses the blood-brain barrier. The concentration in saliva becomes 3.6 times higher than in plasma.¹¹

There are several producers of PHO and the international sales are monitored by the United Nations International Narcotics Control Board (www.incb.org). Purchases of PHO vary considerably between countries. Australia, United Kingdom, France, and Norway are among the highest consumers, whereas Denmark, Sweden, Germany, and the United States are examples of nonconsuming nations.

As an allergen, the authors' studies have shown PHO to contain one QAI epitope in addition to being monovalent for another allergenic epitope it shares with MOR.¹⁰ NMBAs, like SUX, are structurally bivalent for the QAI epitope (see **Fig. 1**).

In Norway, PHO has been available in the cough mixture Tuxi from one producer (Weifa AS, Oslo, Norway). It has been on the market since 1966 in varying formulations and was largely purchased over the counter, but has not been available in Sweden. Estimates based on sales data indicate that approximately 40% of the Norwegian population has been exposed.

These findings provided the basis for the authors' "pholcodine hypothesis," suggesting that a high consumption of PHO-containing cough mixtures could be related to a high prevalence of IgE-sensitization to PHO, MOR, and, in part, to SUX (ie, QAI);

and, as a consequence, higher frequencies of IgE-mediated, NMBA-induced anaphylaxis.

THE EFFECT OF PHOLCODINE EXPOSURE ON IGE PRODUCTION

A pilot study aimed at exploring the effect on IgE production, in IgE-sensitized and nonsensitized individuals, of exposure to cough syrup and environmental chemicals containing PHO-, MOR-, and SUX-related allergen structures was performed. The Tuxi cough mixture was chosen since it contains PHO and was consumed in great quantities in Norway.

Two participants, found to have IgE antibodies to PHO, MOR, and SUX considered related to the previous use of PHO-containing cough mixtures, were recruited from the Section for Clinical Allergology, Department of Occupational Medicine at Haukeland University Hospital in Bergen, Norway. Two other, scientists, one atopic and one non-atopic, who had not used PHO-containing cough syrups and did not have IgE antibodies to PHO, served as controls.

The first week, the subjects took a PHO-free drug (noscaphine and codeine, respectively). After a two-week interval, a PHO-containing drug (Tuxi cough mixture) was taken, at a dose corresponding to 20 mg of PHO, once daily for 7 consecutive days. Serum was collected before the start and 2 weeks after the end of each exposure period. In addition, IgE levels of the two sensitized individuals were followed for a few months.

None of the subjects developed any clinical symptoms or changes in serum levels of IgE or IgE antibodies to the monitored substances during the first control week. However, after 7 days with the PHO-containing cough syrup, the sensitized individuals experienced some clinical symptoms (pruritus and mild localized urticaria), and large increases in the concentration of IgE (60- to 105-fold) (Fig. 2) and IgE antibodies to

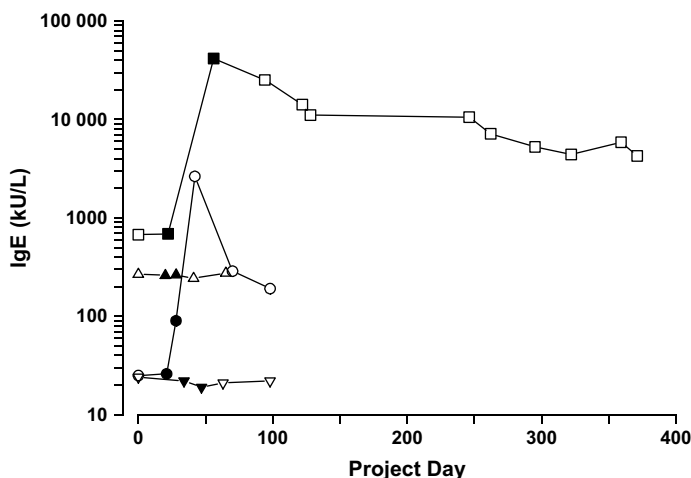


Fig. 2. Serum levels of IgE (kU/L) of person EF (open square), HE (open circle), HÖ (open triangle), and TH (open diamond) before and after oral intake (between filled symbols) of cough syrup containing PHO. (From Florvaag E, Johansson SGO, Öman H, et al. Pholcodine stimulates a dramatic increase of IgE in IgE-sensitized individuals. A pilot study. *Allergy* 2006;61:51; with permission.)

PHO, MOR, and SUX (30- to 80-fold). In contrast, the IgE concentrations of the two nonsensitized controls did not change during noscapine, codeine, or PHO exposure.

Three individuals IgE-sensitized to PHO were exposed to household chemicals selected for containing or lacking PHO, MOR, and SUX allergenic epitopes. They had the questionable pleasure of exposing themselves to PHO-allergens by eating four daily doses of licorice candy totaling 256 g for a week; eating 6 times daily salmiak lozenges, totaling 42 lozenges for another week; and, during the same week, washing their hair three times with L'Oreal Professional Vitamino Color shampoo. As a reference, for a week they enjoyed four daily tablets of Dekadin menthol, which does not contain PHO-allergens. In both cases no increase or significant drop in the concentrations of IgE and IgE antibodies to PHO, MOR, or SUX was seen (Fig. 3). However, compared to other persons who were IgE-sensitized to PHO but had not been this extremely exposed, their IgE levels remained remarkably stable. Thus, it seems as if household chemicals sharing PHO-allergens, including the QAI-epitope, but lacking the unique PHO structure, cannot initiate an IgE-sensitization but can, to some minor degree, stimulate and maintain such an IgE-antibody production.

The results indicated, however, that if an individual IgE-sensitized to PHO is exposed to even small amounts of cough syrups containing PHO, the IgE system is very strongly stimulated.¹² Thus it appeared possible that such cough syrups, by sensitizing and boosting, could put people at risk for developing an allergic anaphylaxis to NMBA.

PHOLCODINE EXPOSURE OF INDIVIDUALS WITH PREVIOUS IGE-MEDIATED NEUROMUSCULAR BLOCKING AGENT ANAPHYLAXIS

A controlled, randomized clinical trial on a population with previously diagnosed IgE-mediated anaphylaxis towards NMBAs was then initiated. The primary aim was to study whether PHO exposure caused changes in serum levels of IgE and IgE antibodies to PHO, MOR, and SUX in a larger number of individuals, thereby corroborating the results from the pilot study.

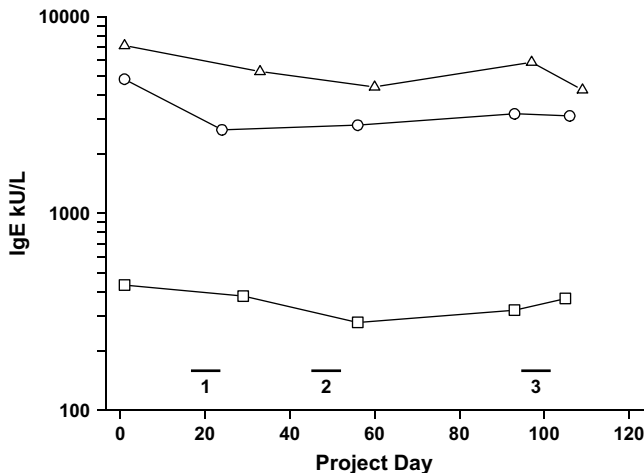


Fig. 3. IgE values in samples from EF (open triangle), LF (open circle) and ÅS (open square) taken before and after the three 1-week household chemical exposure sessions (1, 2, and 3). (From Florvaag E, Johansson SGO, Öman H, et al. Pholcodine stimulates a dramatic increase of IgE in IgE-sensitized individuals. A pilot study. *Allergy* 2006;61:52; with permission.)

Seventeen patients from a previous clinical study on anaphylaxis during general anaesthesia⁸ were recruited at the Haukeland University Hospital in Bergen, Norway. The patients were randomized to ingest one single daily dose, about one-third of that recommended, of the cough syrup Tuxi or guaifenesin (Solvipect, Nycomed Pharma, Asker, Norway). IgE and IgG antibodies to SUX, MOR, PHO, and inhalant and food allergen mixes, were quantified before and 4 and 8 weeks after start of exposure.

There were no significant differences in the concentrations of IgE or IgG antibodies to PHO, MOR, or SUX between the study groups before cough syrup exposure. At 4 weeks after start of exposures, there was a large increase in IgE concentrations in the pholcodine group. No changes were seen in the guaifenesin group. The highest increase occurred with antibodies to SUX, MOR, and PHO; whereas the rise in IgG levels was intermediate. IgG antibodies to inhalant and food allergens also showed some, but only slight elevation.

This study demonstrated that individuals who have suffered anaphylaxis during general anesthesia and are IgE-sensitized to an NMBA respond with a remarkable and statistically highly significant increase in IgE production when exposed to small doses of cough syrup containing pholcodine.⁹

PHOLCODINE-CONTAINING COUGH MIXTURE WITHDRAWN FROM THE MARKET

Based on the result of the authors' studies, the Norwegian producer decided not to renew the marketing license for the PHO-containing cough syrup Tuxi, which was taken off the market in March 2007. This decision was strongly supported by the Norwegian Medicines Agency. The immunologic and clinical consequences of taking PHO off the market are now being studied, although reaching a statistically significant decrease of the low number of NMBA-related anaphylaxis will probably take some time.

However, there are already some indications of what happens when PHO exposure is reduced. Today, after one year without Tuxi, the percentage of sera sent to Haukeland University Hospital allergy laboratory found to have IgE antibodies (>0.35 kU_A/L) to PHO, MOR, and SUX are about half as many as when Tuxi was on the market (E. Florvaag, personal communication, 2008).

It was recently brought to the authors' attention that, during the 1970s and 1980s, a PHO-containing cough syrup, Tussokon, (Pharmacia AB, Uppsala, Sweden) was available in Sweden. It was phased out of the market from 1987 to 1989 because of "changes in recommendations for treatment of cough and because other, more efficient pharmacological preparations had become available" according to the producer. Nothing is mentioned about any possible relation to anaphylaxis during anesthesia. We have managed to find some allergic patients' sera from these years in our freezers. As many as 5% to 6% of the Swedish sera from the 1970s and 1980s have IgE antibodies to PHO.¹³ However, from the 1990s, just 2% positive sera were found; and among 300 sera from 2002¹⁰ and approximately 200 sera from 2005 (Johansson, S.G.O., unpublished data) no PHO-positive sample was found.

INTERNATIONAL STUDY IN PROGRESS

The Norwegian findings prompted continued studies in other countries. Reports of NMBA-induced anaphylaxis are more prevalent in countries like Australia, France, and United Kingdom, which, like Norway, represent high consumers of PHO; than reports from low- or nonconsuming countries like Germany, United States, and Finland. Accordingly, an international study on the connection between PHO consumption and IgE-sensitization in nine countries is presently undertaken and

preliminary data seem to support the PHO hypothesis (Johansson, S.G.O., unpublished data).

NEW OPPORTUNITIES TO PREVENT ANAPHYLAXIS

The accumulating data on the connection between PHO consumption, IgE-sensitization to PHO and SUX, and the prevalence of IgE-mediated anaphylaxis to NMBAs present new opportunities for preventing these dreaded adverse events. Strategies would primarily need to include, as in Norway, the removal of PHO-containing drugs from the many national markets where they are still available. However, according to the broad spectrum of chemicals in the environment causing exposure to the QAI-structure, through the use of drugs, household, or occupational products, it is to be expected that other substances may exist that have similar IgE-stimulating properties. If so, these also need be identified and similarly removed.

OTHER CLINICAL CONSEQUENCES OF IGE-SENSITIZATION TO PHO

From recent years of clinical practice at the Center for Clinical Allergology in Bergen, Norway, the authors have been confronted with two types of diagnostic challenges now looked upon as typical consequences of PHO-sensitization. The first is referrals for high serum levels of "total IgE" from about 1,000 kU/L and above. These IgE levels, which could not be explained by severe clinical allergy or other causes (eg, active atopic eczema, parasitic infestations), are associated with a high frequency of IgE antibodies to PHO.

Likewise are referrals of patients without any significant clinical symptoms, but where the GP has requested and found a number of low-level serum IgE-antibodies to airway and food allergens. Serological exploration of such cases often end up with finding considerable elevated "total IgE" and IgE-antibodies to PHO. Based on the PHO hypothesis the correct approach in these two situations is to clarify whether PHO-containing medicines have been used, to stop further exposure, and to follow up with serological normalization. A third challenge in PHO-sensitized individuals is related to the treatment options in severe allergic asthma. The decision whether anti-IgE treatment is indicated, and the calculation of the correct dose is partly based upon the measured levels of serum IgE. The effect of PHO on this variable may therefore influence decision outcomes in such cases.

SUMMARY

Considerable support for the PHO hypothesis has been established and several studies with new and complementary data are under way. The hypothesis carries promising prospects for the prevention of IgE-mediated anaphylaxis to NMBAs.

PHO works in rare and subtle ways, and the mechanism of effect on IgE-synthesis is not known. As a MOR-analogous antitussive, and structurally a monovalent hapten with two independent allergenic epitopes, it only very rarely gives rise to severe IgE-mediated allergic reactions towards itself. However, it does so considerably more often to quite a different group of drugs—the NMBAs, which are bivalent to the QAI-containing epitope and, thus, structurally complete allergens. The use as a cough depressant and cold medicine, which to a considerable degree is sold over the counter, allows its distribution and potential sensitization to become widespread in populations.

Alarming, IgE-sensitization and extremely high levels of IgE-antibodies can virtually go clinically unnoticed until the unfortunate individual suddenly needs an, often

immediate, surgical intervention. The rapid induction of general anesthesia under such circumstances, to avoid aspiration of gastric contents during intubation, is often done by the use of a quick acting NMBA such as SUX. By intravenous injection, the allergenic drug rapidly gains a general distribution in the unknowingly sensitized victim. This is an extremely unfortunate situation and one that, within minutes, may dramatically challenge the qualifications of the responsible anesthetist and threaten patient safety.

Following such adverse events considerable uncertainty may exist as how to safely administer a successive general anesthesia to the patient if needed at a later time in life. Good advice can only be obtained after thorough examinations. First, analysis of serum drawn in close relationship to the reaction documented by an increased serum tryptase should be followed by a standardized, allergological follow-up investigation. It is important to examine carefully all the drugs used during induction and maintaining of anesthesia, as well as other drugs administered and additional exposures that may take place in the operating theater.

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