SelfCare
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OPINION

SelfCare 2012;**3**(1):2-14

PHOLCODINE-CONTAINING COUGH MEDICINES AND ANAPHYLACTIC REACTIONS DURING SURGERY

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ABSTRACT

Cough medicines containing pholcodine (PHO) are used to suppress unproductive coughs and have been available as non-prescription products in many countries worldwide for decades. Recently, concerns have been raised about the safety of these products based on a body of evidence which purports to show a relationship between the use of pholcodine and the incidence of anaphylactic reactions to anaesthetic drugs.

The striking historical difference in apparent rates of anaphylaxis to neuromuscular blocking agents (NMBAs) in Norway and Sweden was the original stimulus to develop the 'pholcodine hypothesis'. At that time pholcodine was not available in Sweden but consumption in Norway was high. The finding that pholcodine was a potent stimulus to IgE production, and the apparent cross - reactivity of this IgE with suxamethonium, led some Scandinavian researchers to propose that consumption of pholcodine explained the observed difference in anaphylaxis incidence across this border between otherwise similar populations. Subsequent withdrawal of pholcodine containing preparations from the market in Norway was said to have led to a reduction of NMBA related anaphylaxis in that country.

This review examines factors affecting the risks of anaphylaxis to NMBAs during surgery and critically evaluates the evidence supporting the 'pholcodine hypothesis'. Unresolved issues and gaps in the current evidence base supporting a role for pholcodine in these reactions are examined.

As well as studies to examine the possible association with phlocodine, further research may be needed into other possible mechanisms of IgE-mediated allergic anaphylaxis to NMBAs, in patients not previously exposed to them. Calls to restrict the availability of useful medicinal substances should be based on firm evidence of risk rather than associations with unproven causality.

Key words: Pholcodine, cough suppressant medicines, neuromuscular blocking agents, anaphylaxis, anaesthesia.

INTRODUCTION

In February 2011 the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) began an examination of pholcodine (PHO) containing medicines prompted by observations suggesting that there may have been a decrease in anaphylactic reactions to NMBAs in Norway coinciding with the withdrawal of pholcodine from the market in that country. The researchers responsible for those studies hypothesized that the use of pholcodine

Accepted for publication 03 February 2012

containing medicines, through stimulation of IgE production which cross reacts with other drugs containing a substituted ammonium ion, increases the risk of allergic responses to NMBAs.

Recently the CHMP concluded that it found '... no firm evidence to substantiate the hypothesis of cross-sensitisation between pholcodine and NMBAs and a subsequent increased risk of anaphylactic reactions during surgery'. However the committee proposed that companies conduct post marketing studies to investigate further the possibility of an association between pholcodine and anaphylactic reactions to NMBAs. A press release summarising the outcome of this safety review can be accessed at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Pholcodine_31/WC500117795.pdf

This review examines the evidence which prompted the CHMP review and in particular critically evaluates the 'pholcodine hypothesis' which proposes a link between the widespread use of this ingredient in cough medicines and risk of anaphylaxis during surgery

RISK OF ANAPHYLAXIS DUE TO NMBAS IN SURGERY

Causes and epidemiology of anaphylaxis in surgery

Anaphylaxis has been defined as 'a severe, life-threatening, generalized or systemic hypersensitivity reaction'[1]. The European Academy of Allergy and Immunology[2], and the World Allergy Organisation, have proposed that anaphylactic-type reactions should be classified into *allergic anaphylaxis* and *nonallergic anaphylaxis*, allergic reactions being sub-divided into *IgE-mediated* and *non-IgE-mediated* reactions.

Based on studies in Australia and France, the overall incidence of anaphylaxis during anaesthesia has been estimated at between 1 in 10 000 and 20 000 procedures[3,4]. Around 10% of anaesthesia-related reactions reported to the UK Medicines and Healthcare Products Regulatory Agency (MHRA) were fatal[5]. However incidence data should be interpreted with caution because the denominator is uncertain, since it is likely that many less severe reactions during surgery are not reported (see below). In a study of the mortality rate due to anaesthesia based on the analysis of death certificates from the national mortality database in France for 1999, only 3 deaths related to an allergic reaction were identified[6]. Whatever the true figure, the low incidence of anaphylactic reactions poses obvious difficulties in studying the effects of individual drugs even using national databases.

Adequate muscle relaxation is essential for many surgical procedures and is also a vital component of anaesthetic technique to facilitate endotracheal intubation and treat laryngeal spasm. However the use of neuromuscular blocking agents (NMBAs) in surgery is associated with rare but potentially serious anaphylactic reactions. In one large study an immune basis was demonstrated in two-thirds of patients investigated for anaphylaxis[7]: the remainder comprised nonallergic anaphylaxis and reactions other than anaphylaxis. In most published

Accepted for publication 03 February 2012

series, NMBAs represent the most frequently involved substances, accounting for 50 to 70% of cases. Allergic reactions induced by NMBAs are almost exclusively IgE-mediated[8].

Neuromuscular blocking drugs appear to cause anaphylaxis more commonly in female patients. In all series of reactions to neuromuscular blocking agents, there is a significant female predominance varying from 2:1 to 4:1, even when possible differences between the number of anesthetic procedures performed on men and women is taken into account[8].

Individuals with a history of atopy, asthma or allergy to some foods appear to be at increased risk of latex allergy but not anaphylactic reactions to neuromuscular blocking drugs or antibiotics during surgery. Patients with asthma may suffer a more severe reaction because bronchospasm is more likely to be a feature. Some of these reactions may be refractory to conventional therapy[9].

Recognition and clinical diagnosis of anaphylaxis in surgery

The true incidence of anaphylactic reactions and their associated morbidity and mortality is difficult to define with confidence, but anaphylaxis during anaesthesia is likely to be underestimated. In a closely monitored patient during anaesthesia, when a fall in blood pressure, change in heart rate or difficulty with ventilation is noted, anaphylaxis is so rarely the cause that treatment is often given for another diagnosis before an allergic cause is suspected. Subsequently, the response to this treatment may delay or even prevented recognition of the true cause. It is therefore probable that many grade I and II acute allergic reactions to anaesthetic drugs are missed[9].

Table 1: Grades of allergic reaction during anaesthesia

Grade	Signs
I	Cutaneous signs: generalized erythma, urticaria, angioedema
II	Measurable but not life-threatening symptoms Cutaneous signs, hypotension, tachycardia Respiritory disturbance: cough, difficulty to inflate
III	Life-threatening symptoms: collapse, tachycardia or brady-cardia, arrhythmias, bronchospasm
IV	Cardiac and/or respiratory arrest

Conversely, a cause other than allergic anaphylaxis seems more likely in around one-third of patients referred to specialist centres for investigation of suspected anaphylaxis during anaesthesia[7].

Guidelines emphasize that although the presence of drug-specific IgE in serum is evidence of allergic sensitization in that individual, it is not in itself proof that the drug is responsible for

Accepted for publication 03 February 2012

the reaction. Attribution of cause and effect is a balanced judgment made after considering all the clinical and laboratory information relevant to the reaction[9].

IgE mediated anaphylaxis with NMBAs

In up to 50% of cases, IgE-mediated anaphylaxis to NMBAs has been reported despite no known previous exposure to a NMBA. Anaphylaxis after a first-time NMBA administration suggests a possible cross-reaction with IgE antibodies generated by previous contact with apparently unrelated chemicals. There is strong evidence that quaternary ammonium ions (QAI) are the allergenic determinants in NMBAs. These small and ubiquitous structures occur widely in many drugs but also in foods, cosmetics, disinfectants and industrial materials [8,10]. In daily life, numerous opportunities may present for a predisposed individual to become sensitized to QAIs and thus at risk of developing anaphylaxis to NMBAs during anaesthesia[10].

In antibody combining site studies of the specificity of IgE antibodies that react with NMBAs, a variety of drugs containing tertiary and/or quaternary ammonium groups with different pharmacological activities were shown to strongly inhibit antibody binding to an NMBA. A number of alkaloids with different actions and drugs with antihistamine, antipsychotic, anticholinesterase, ganglionic blocking, narcotic, local anesthetic, antibiotic, and other actions, cross-react with IgE antibodies that recognize NMBDs, indicating the wide range of possible sources for sensitization of patients on medication[8,10].

Sensitization to substances containing a single substituted ammonium ion is most often silent, (although minor skin reactions may go un-noticed) and serious allergic responses have been reported only rarely. Conversely the probable explanation for the relatively frequent involvement of NMBAs in anaphylaxis relates to their molecular structure. The substituted ammonium ions of NMBAs appear to be responsible for both the neuromuscular blocking and allergenic properties of these drugs. As there are at least two of these groups at a distance apart of from 1 to 1.45 nm, it has been suggested that NMBAs elicit allergic mediator release by binding to and bridging combining sites of adjacent cell-bound complementary IgE molecules via their ammonium groups. It is likely that other structure-activity related determinants of allergenicity are also important[10].

The prevalence of sensitization to NMBAs in the community is higher than the incidence of allergic reactions would suggest. In one study, approaching 10% of the general population exhibited skin reactivity to NMBAs, an incidence that far exceeds the incidence of anaphylaxis on administration of these drugs during anaesthesia[9]. On the other hand, an uneventful exposure during surgery may sensitize an individual to subsequent administration of the NMBA.

Cross-sensitivity between different NMBAs is relatively common because they all share a quaternary ammonium epitope. Whether some NMBAs are more likely than others to cause anaphylaxis is controversial. Very large sample sizes would be needed to estimate the true incidence of reactions to individual drugs: e.g. if the true incidence is 1 in 5000, a sample size

Accepted for publication 03 February 2012

of 7 million would be needed to have a 95% chance of being within 5% of the true value[9].

The 'pholcodine hypothesis'

The pholcodine hypothesis arose from observations and experiments performed over a number of years by a group in Scandinavia. The Norwegian Network for Anaphylactic Reactions during Anaesthesia (NARA) was started in 1998 and established standardized national routines for immediate and follow-up diagnostic investigations of probable cases. The first Norwegian clinical report from the Bergen centre found 83 cases of anaphylaxis during a 6-year period. A frequency of one anaphylactic reaction per 5,200 general anesthesia events where NMBAs were administered was found and 71.1% of the reactions were classified as IgE-mediated, of which 93.2% were related to NMBAs (principally suxamethonium [SUX] or rocuronium). It was 'estimated from in-hospital data' (although no further details are given) 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[11].

The prevalence data for Norway based partly on official spontaneous reports and partly on this 6-year single center study, suggested that anaphylactic reactions to NMBAs were approximately 10 times higher in Norway than in Sweden. Although differences in reporting were possible, the authors speculated that it was conceivable that the two populations were differently exposed to an unknown environmental factor that gave rise to production of IgE antibodies with specificity for the QAI-epitope.

While establishing a radioimmunoassay for morphine (MOR) the authors 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. Competitive binding studies established that these were epitope-specific and not caused by any unspecific mechanism. The authors speculated that allergic Norwegians may have become IgE-sensitized to MOR through exposure to an unknown environmental factor.

This prompted the authors to use the socially and geographically closely related countries Norway and Sweden as a research model. Studies were initiated 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.

To look for the putative 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 Morphine (MOR) and SUX-sensitized and non-sensitized individuals in Norway and Sweden[12]. 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 drug exposures, the authors concluded that the populations in the two countries were exposed to the same

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compounds, although to different degrees. However, the authors noted one exception: the use in Norway, but not in Sweden, of a cough mixture that, in contrast to all other drugs, contained pholcodine (PHO).

The authors then decided to perform a comparative study to document 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 and compared to sera from patients with a documented IgE-mediated, NMBA-initiated anaphylactic reaction.

Three hundred consecutive samples from volumes left after analyses for IgE antibodies requested by physicians referring for investigation of atopy were collected from one laboratory in each country. In addition, serum samples from over 500 blood donors in each country were examined. 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 IgE 'sensitized' to SUX; as were 5%, 10%, and 66.7%, respectively, to MOR. Among blood donors and allergic patients from Sweden, none with IgE antibodies to SUX or MOR was found. IgE antibodies to PHO were found in 6% of blood donors from Norway, but in none from Sweden[12].

As an allergen, these authors and others had shown PHO to contain one QAI epitope in addition to being monovalent for another allergenic epitope it shares with MOR. As noted previously, NMBAs, like SUX, are structurally bivalent for the QAI epitope.

The authors noted that purchases of PHO-containing products 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 non-consuming nations.

In Norway, PHO was available in the cough mixture Tuxi® from one producer since 1966 in varying formulations and was largely purchased over the counter, but this medicine had not been available in Sweden since the 1980's. Estimates based on sales data indicated that an extraordinarily high proportion (40%) of the Norwegian population had been exposed to PHO from this one product. These findings led the authors to propose a 'pholcodine hypothesis,' 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 that this might explain higher frequencies of IgE-mediated, NMBA-induced anaphylaxis.

The authors then performed a pilot study[13] to explore the effect of exposure to Tuxi® cough syrup and environmental chemicals containing PHO, MOR-, and SUX-related allergen structures on IgE production, in IgE-sensitized and non-sensitized individuals. Two participants, found to have IgE antibodies to PHO, MOR, and SUX considered related to the previous use of PHO-

Accepted for publication 03 February 2012

containing cough mixtures, were recruited. Two other individuals, 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. After 7 days consuming 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) and IgE antibodies cross-reacting to PHO, MOR, and SUX (30- to 80-fold). In contrast, the IgE concentrations of the two non-sensitized controls did not change during PHO exposure.

Three individuals IgE-sensitized to PHO were exposed to household chemicals selected for containing or lacking PHO, MOR, and SUX allergenic epitopes. No increase or significant drop in the concentrations of IgE and IgE antibodies to PHO, MOR, or SUX was seen. Compared to other persons who were IgE-sensitized to PHO but had not been this extremely exposed, their IgE levels remained remarkably stable. The authors concluded that these household chemicals sharing PHO-allergens, including the QAI-epitope, but lacking the unique PHO structure, cannot initiate an IgE-sensitization but might, to some degree, stimulate and maintain such an IgE-antibody production.

The authors concluded that it was possible that PHO-containing cough syrups, by sensitizing and 'boosting', could put people at risk for developing an allergic anaphylaxis to NMBA.

The authors then undertook a controlled, randomized clinical trial[14] on a population with previously diagnosed IgE mediated anaphylaxis towards NMBAs, 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, to confirm the results from the pilot study. Seventeen patients from a previous clinical study on anaphylaxis during general anaesthesia were recruited and randomized to ingest one single daily dose, about one-third of that recommended, of the cough syrup Tuxi® or guaifenesin.

There were no significant differences in the concentrations of IgE or IgE antibodies to PHO, MOR, or SUX between the study groups before cough syrup exposure. At 4 weeks there was a large increase in IgE concentrations in the Tuxi® (pholcodine) group. No changes were seen in the guaifenesin group. This study demonstrated that individuals who have suffered anaphylaxis during general anesthesia and are IgE-sensitized to an NMBA respond with a statistically highly significant increase in IgE production when exposed to small doses of cough syrup containing pholcodine.

Two important recent studies by the same authors and relevant to the hypothesis have been published:

In the first, Florvaag *et al*[15] describe a study performed to examine the effects of the withdrawal of Tuxi® cough syrup from the market in Norway during 2007. Three hundred sera from allergic patients were sampled yearly from 2006 through to 2010 and analyzed for IgE antibodies reactive to PHO, SUX and morphine. Results of IgE tests and preliminary

Accepted for publication 03 February 2012

reports from the Norwegian Network for Anaphylaxis under Anaesthesia (NARA) were also monitored. Following PHO withdrawal, within 1 year, prevalence of antibodies to PHO and SUX fell significantly from 11.0% to 5.0% and from 3.7% to 0.7%, respectively. It is notable that proportions exhibiting cross reactivity to SUX were considerably higher in groups with 'Medium' (1,000-5,000 kU/l) or 'High'(>5,000 kU/l) IgE titers (12%, n= 100, and 30.6% n= 49, respectively). However, without correction for total IgE[16], the degree to which non-specific binding contributed to this cross sensitization cannot be known.

After 3 years, the authors concluded that incidence of reported suspected anaesthetic anaphylaxis fell significantly, both the total number, the reactions related to NMBAs and those with IgE antibodies to SUX. However it is apparent from data tabulations in the paper that numbers of suspected reactions in 2008 (n=88) were similar to 2006 and 2007 (n=89 and 81 respectively), so the positive trend for reduction relies on results from 2009 (n=53) and the first 6 months of 2010 (n=25). The conclusions from these early years must be regarded as tentative until further data are collected. Furthermore the absolute number of reactions associated with IgE SUX sensitivity (sera with IgE antibodies to SUX (> 0.35 kU/l) is small (12, 15 and 3 for 2007, 2008 and 2009 respectively) and does not appear to account for the total reduction in NMBA associated reactions (n= 56, 66 and 34 for 2007, 2008 and 2009 respectively). The association of these findings with IgE sensitization to SUX as a result of PHO exposure cannot be assumed to be causative.

Johansson *et al*[17] recently reported the results of a multinational examination of the pholcodine hypothesis, i.e. that the consumption of PHO-containing cough mixtures could cause higher prevalence of IgE antibodies to PHO, morphine (MOR) and suxamethonium (SUX) and thereby potentially increase the risk of NMBA associated anaphylaxis. National PHO consumptions were derived from the United Nations International Narcotics Control Board (INCB) database. IgE and IgE antibodies to PHO, MOR, SUX and P-aminophenyl-phosphoryl choline (PAPPC-another quaternary ammonium assay) were measured in sera from atopic individuals collected in nine countries representing high and low PHO-consuming nations.

There was a significant positive association between PHO consumption and prevalences of IgE-sensitization to PHO and MOR, but not to SUX and PAPPC, as calculated both by exposure group comparisons and linear regression analysis. The Netherlands and the USA did not have PHO-containing drugs on the market, although the former had a considerable PHO consumption. Both countries had relatively high figures (4.9% and 2% respectively) of IgE-sensitization to pholcodine (i.e. raised IgE antibody levels to PHO).

The authors concluded that this international prevalence study 'lends additional support to the PHO hypothesis', although this might be regarded as a selective view of the results. The authors conceded that the results also indicated that other, as yet unknown, substances may lead to IgE-sensitization towards NMBAs.

Accepted for publication 03 February 2012

This study produced some findings which are difficult to reconcile with the pholcodine hypothesis:

- The USA, where no PHO is consumed, exhibited a similar level of IgE sensitivity to PHO as the UK (2.0 and 2.4% respectively) which has PHO consumption second only to France.
- No IgE reactive to SUX was seen in the UK despite the high PHO consumption in that country.
- Of 4 the countries with antibodies to SUX, the USA (2.5%) and Germany (0.5%) have no PHO consumption.
- The Netherlands, Finland and the UK had 4.9, 1 and 2.4% of samples respectively exhibiting IgE reactive to PHO, but no samples reactive to SUX.

Only France and Norway (based on historical data) exhibited high consumption of PHO and raised proportions of subjects with IgE sensitive to both PHO and SUX. Only when results from the Netherlands (uncertain PHO consumption) and USA (no PHO consumption) were excluded was a statistically significant association between PHO consumption and IgE-sensitization to PHO (P = 0.010), MOR (P = 0.004) and SUX (P = 0.032) seen on linear regression analysis. It seems selective to regard these results as supportive of the pholcodine hypothesis, when this does not explain other observed results.

Pholcodine-containing anti-tussives are readily available in Belgium, although consumption per capita is four times less than previously seen in Norway. In a series examining IgE titers in patients with a confirmed NMBA sensitivity and a control group, almost no IgE antibodies against suxamethonium and pholcodine were demonstrable in control individuals. In this survey, apart from in the patients, positive IgE tests for these drugs were almost exclusively observed in sera with elevated titers of total IgE. This led the authors to question the clinical relevance of IgE cross – sensitivity findings in the absence of total IgE titers[16].

SUMMARY

The overall incidence of anaphylaxis in surgery is very low (although it is probably underreported). The true incidence of anaphylactic reactions and their associated morbidity and mortality remain poorly defined due to uncertainties regarding the completeness of the data collected. Accordingly, apparent changes in incidence of anaphylactic reactions in individual countries over relatively short intervals need to be interpreted with considerable caution. The recent data from a study[15] of the effect of PHO withdrawal in Norway on rates of anaphylactic reactions during anaesthesia should be regarded as preliminary and not conclusive regarding a causative link.

The striking historical difference in apparent rates of anaphylaxis to NMBAs in Norway and Sweden was the original stimulus to develop the 'pholcodine hypothesis'. At that time pholcodine

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was not available in Sweden but consumption in Norway was high. The finding that pholcodine was a potent stimulus to IgE production, and the apparent cross-reactivity of this IgE with suxamethonium, led some researchers to propose that consumption of pholcodine explained the observed difference in anaphylaxis incidence across this border between otherwise similar populations.

The pholcodine hypothesis has received considerable attention, however there are a number of unresolved questions regarding NMBA – induced anaphylactic reactions which cannot be accounted for by this hypothesis. Additionally there are other findings which are in conflict with the 'pholcodine hypothesis' or cast doubt on the generalisability of the experience in Norway and Sweden.

The breadth of pholcodine exposure in Norway before its withdrawal was extremely high (estimated at over 40% of the population) and was predominantly as a result of consumption of one pholcodine-containing preparation. This per capita level of usage is seen in only two other European countries (France and UK), and in most countries a variety of pholcodine preparations of differing formulations are available. Therefore direct extrapolation from the experience in Norway to other European countries may be unreliable. A recent international survey[18] showed IgE antibody titers reacting to pholcodine and suxamethonium in countries where pholcodine was not available. This strongly suggests that at least some of the IgE reacting to PHO (and cross-reacting to suxamethonium) is generated in response to other substances in the environment.

The sensitivity of tests for NMBA cross–reactivity of IgE raised in response to pholcodine is affected by high total titers of IgE[16,10]. In the absence of total IgE quantification in the studies by Florvaag *et al.*, interference due to raised total IgE cannot be excluded.

The marked preponderance of females in reactions to NMBAs (from 2:1 to 4:1 *vs* males) is unexplained. If previous exposure to pholcodine-containing cough medicines was the most important determinant of risk for NMBA anaphylaxis, it is unlikely that this would operate differently according to gender. Conversely some other QAI-containing substances in the environment, e.g. cosmetics or certain shampoos, might plausibly be associated with a gender difference in exposure.

Surveys of potential environmental sources of increased sensitivity to muscle relaxants are lacking. In perhaps the only comprehensive study so far attempted, Florvaag *et al.* examined 84 different household and other environmental chemicals and formulations in IgE antibody inhibition tests to morphine and succinylcholine. Cross-reactivity was detected in skin and hair care preparations, toothpastes, cough syrups, lozenges and household cleaners and some products inhibited in both assays. However the lack of quantification and standardization of extracts used in these inhibition experiments and the absence of an adequate list of components in the agents examined makes interpretation of the results difficult.

Accepted for publication 03 February 2012

Exposure to medications and chemical agents encountered in the household and/or workplace may be the most obvious explanation of allergic sensitization to NMBAs, however it would be wrong to assume that other mechanisms are not plausible causes or contributory factors. Findings in other fields have led to two other speculated mechanisms described in a 2009 learned review[10] of the immunochemical basis of this phenomenon:

1. *Antigens containing phosphorylcholine, sometimes called 'C-substances', have been found widely distributed in bacteria, fungi, protozoa, plants, arthropods and parasitic worms. Purified 'C-substances' isolated from a number of allergenic sources including house dust mites, helminths, nematodes and fungi, have been shown to be allergenic in IgE antibody binding and histamine release studies. Antigenic substances containing the tertiary ammonium compound phosphorylcholine are widespread and frequently allergenic, eliciting IgE antibody responses. This, and the well-known occurrence of antibodies complementary to phosphorylcholine, all suggest that this compound, perhaps as a determinant on any of a number of different 'C-substances', may be the stimulating antigen of the IgE anti-ammonium antibodies in NMBD-allergic subjects. Immunochemical investigations could be devised to test the veracity or otherwise of this speculation.*

2. *Mammalian rhesus proteins and ammonium transport Mammalian rhesus (Rh) proteins that carry the Rh blood group antigens show some homology to the ammonium channel (Amt) proteins found in both prokaryotes and eukaryotes. Three of the five human Rh proteins transport ammonium across the plasma membrane while the other two may bind it without transporting it. Organisms such as fungi (e.g. Aspergillus sp.) and intestinal worms (e.g. Ascaris sp.) are highly allergenic and may provoke allergic symptoms ranging from mild to anaphylactic and with accompanying high serum IgE antibody evels. It has been suggested that the IgE class of antibody arose as a defence against such organisms. The existence of Amt proteins in fungi and parasitic worms suggests the possibility of an IgE antibody response to an Rh-ammonium ion complex with at least some of these antibodies complementary to the cell-bound ammonium ions. Again, this speculative theory for the origin of NMBD-reactive IgE antibodies is amenable to experimental testing. In the first instance it would be interesting to examine and compare the Rh status of NMBD-allergic and control subjects.*

Further investigations are needed to establish the cause for NMBA sensitivity reactions in patients without prior exposure to these agents. The immunological basis of these serious anaesthetic events appears to involve another allergenic determinant in the environment, but whether this is one drug or a class of more ubiquitous substances remains speculative.

The CHMP has recently called for a case-control study to further investigate the association between NMBA allergic reactions and pholcodine consumption, while concluding that at present there is insufficient evidence to support the pholcodine hypothesis.

Accepted for publication 03 February 2012

CONCLUSION

This review has illustrated that there remains considerable uncertainty regarding the validity of the 'pholcodine hypothesis' which suggests that consumption of pholcodine containing cough medicines increases the risk of NMBA-related anaphylactic reactions during surgery. Taken as a whole, the evidence for this hypothesis remains inconclusive and a causative link between the effects of pholcodine and differential rates of NMBA-associated anaphylaxis across international borders has not been established. Unless further evidence of causation is forthcoming, calls for restrictions on the availability of widely used cough medicines containing pholcodine cannot be justified.

Conflict of Interests: This paper is based on a report commissioned and paid for by the Proprietory Association of Great Britain. Dr Stephen Mann is an independent pharmaceutical consultant.

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REFERENCES

1. Johansson SGO, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. Journal of Allergy and Clinical Immunology 2004; 113: 832–6.
2. Johansson SG, Hourihane JO, Bousquet J, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. Allergy 2001; 56: 813-24.
3. Fisher MM, Baldo BA. The incidence and clinical features of anaphylactic reactions during anesthesia in Australia. Annales Francaises d'Anesthesie et de Reanimation 1993; 12: 97–104.
4. Laxenaire MC. Epidemiology of anesthetic anaphylactoid reactions. Fourth multicenter survey (July 1994-December 1996). Annales Francaises d'Anesthesie et de Reanimation 1999; 18: 796–809.
5. Axon AD, Hunter JM. Editorial III: Anaphylaxis and anaesthesia – all clear now? British Journal of Anaesthesia 2004; 93: 501–4.
6. Lienhart A, Auroy Y, Pequignot F, et al. Survey of anesthesiarelated mortality in France. Anesthesiology 2006; 105: 1087-97.
7. Mertes PM, Laxenaire MC, Alla F. Anaphylactic anaphylactoid reactions occurring during anaesthesia in France in 1999–2000. Anesthesiology 2003; 99:536–45.
8. Mertes PM, Aimone-Gastin I, Guéant-Rodriguez RM, Mouton-Faivre C, Audibert G, O'Brien J, Frendt D, Brezeanu M, Bouaziz H, Guéant JL. Hypersensitivity reactions to neuromuscular blocking agents. Curr Pharm Des. 2008;14(27):2809-25. Review.
9. Association of Anaesthetists of Great Britain and Ireland. Suspected anaphylactic reactions associated with anaesthesia. Anaesthesia 2009; 64: pages 199-211
10. Baldo BA, Fisher MM, Pham NH. On the origin and specificity of antibodies to neuromuscular blocking (muscle relaxant) drugs: an immunochemical perspective. Clin Exp Allergy. 2009 Mar;39(3):325-44. Review.

Accepted for publication 03 February 2012

11. Florvaag E, Johansson SG. The Pholcodine story. Immunol Allergy Clin North Am. 2009 Aug;29(3):419-27.

12. Florvaag E, Johansson SGO, Oman H et al. Prevalence of IgE antibodies to morphine. Relation to the high and low incidences of NMBA anaphylaxis in Norway and Sweden, respectively. Acta Anaesthesiol Scand 2005; 49:437–44.

13. Florvaag E, Johansson SGO, Oman H, et al. Pholcodine stimulates a dramatic increase of IgE in IgE-sensitized individuals. A pilot study. Allergy 2006;61:49–55.

14. Harboe T, Johansson SGO, Florvaag E, et al. Pholcodine exposure raises serum IgE in patients with previous anaphylaxis to neuromuscular blocking agents. Allergy 2007;62:1445–50.

15. Florvaag E, Johansson SG, Irgens A, de Pater GH. IgE-sensitization to the cough suppressant Pholcodine and the effects of its withdrawal from the Norwegian market. Allergy. 2011 Jan 17.

16. Ebo DG, Venemalm L, Bridts CH et al. Immunoglobulin E antibodies to rocuronium. A new diagnostic tool. Anesthesiology 2007; 107:253–9.

17. Johansson SG, Florvaag E, Oman H, Poulsen LK, Mertes PM, Harper NJ, Garvey LH, Gerth van Wijk R, Metso T, Irgens A, Dybendal T, Halsey J, Seneviratne SL, Guttormsen AB. National Pholcodine consumption and prevalence of IgE-sensitization: a multicentre study. Allergy. 2010 Apr;65(4):498-502.

Accepted for publication 03 February 2012