

Original article

Pholcodine stimulates a dramatic increase of IgE in IgE-sensitized individuals. A pilot study

Background: A previous study showed a relation between pholcodine (PHO) consumption, prevalence of IgE-sensitization to PHO, morphine (MOR) and suxamethonium (SUX) and anaphylaxis to neuromuscular blocking agents (NMBA). The purpose of this pilot study was to explore 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 allergenic structures.

Methods: Serum concentrations of IgE and IgE antibodies to PHO, MOR and SUX allergens measured by ImmunoCAPTM (Pharmacia Diagnostics, Uppsala, Sweden) were followed after intake of cough syrup, or exposure to confectionary and other household chemicals containing various amounts of substances cross-reacting with PHO, MOR and SUX.

Results: Cough syrup containing PHO gave, in sensitized individuals, within 1–2 weeks, an increase of IgE of 60–105 times and of IgE antibodies to PHO, MOR and SUX in the order of 30–80 times. The tested confectionary did not have any similar stimulating effect but seemed to counteract the expected decrease of IgE. No effect was seen in nonsensitized individuals. The PHO stimulated IgE showed a nonspecific binding to ImmunoCAP with common allergens and glycine background ImmunoCAP that was up to 10-fold higher than that of monomeric myeloma-IgE at twice the concentration.

Conclusions: It seems as cough syrups containing PHO have a most remarkable IgE boosting effect in persons IgE-sensitized to PHO, MOR and SUX related allergens. Household chemicals containing such allergenic epitopes seem capable of some, minor, stimulation.

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Anaphylactic reactions, presumably allergic, to curare-like neuromuscular blocking agents (NMBAs) are considerably more common in Norway than in Sweden. Reports indicate at least six times higher prevalences (1, 2), attributed to varying degrees of IgE-sensitization in the otherwise comparable countries (2). Common chemicals in the environment like shampoos, washing detergents, toothpastes and cough medicines share the proposed culprit allergenic epitopes, the quaternary ammonium ions (QAI), with the NMBAs (2). Thus, numerous possibilities exist for a disposed individual to be exposed, get sensitized to QAI and become at risk to develop an allergic anaphylaxis to NMBAs during anaesthesia.

In a recent survey (2) the only significant difference in environmental chemicals exposure found was the use of certain cough medicines. In Norway, but not in Sweden, cough syrups containing pholcodine (PHO) were available and allowed to be accessed without prescription, OTC. As possible consequence, individuals with IgE

antibodies to PHO were common in Norway but very rare in Sweden, e.g. 6.0 and 0%, respectively, of blood donors (2).

The aims of this pilot study were to explore the effects of intake of a PHO containing cough mixture on serum levels of IgE and IgE antibodies to PHO and QAI-related allergens in previously PHO exposed and sensitized individuals compared to un-sensitized controls and to investigate any similar effects of exposure to household chemicals.

Material and methods

Patients and controls

Participants were recruited among patients referred to the Centre for Occupational and Environmental Allergy, Haukeland University Hospital, Bergen, Norway and found to have IgE antibodies to PHO, morphine (MOR) and/or suxamethonium (SUX) considered related to use of PHO containing cough mixtures. Three

patients (HE, LR and ÅS) and one of the authors (EF) were invited to participate in a PHO and/or household chemical exposure study (see below). In addition, two of the authors (HÖ and TH), one atopic and one nonatopic, who had not used PHO containing cough syrups, served as controls in the PHO exposure study.

Exposure tests

PHO containing cough mixture. The sensitized individuals (EF and HE) and the controls (HÖ and TH) were, during 1 week, exposed to a PHO-free drug. HE, HÖ and TH ingested daily one oral dose of 33 mg noscapine (Noskapi[®], Nycomed Pharma, Oslo, Norway) and EF 25 mg codeine (Kodein[®], Nycomed Pharma, Oslo, Norway). After 2 weeks free interval, 10 ml of Tuxi[®] (Weifa AS, Oslo, Norway), corresponding to 20 mg PHO, was taken once daily for 7 days. Serum was collected before start, 2 weeks after end of each exposure period, and 24 h after the last dose of Tuxi. In addition, IgE levels of the two sensitized individuals were followed for several months. The study protocol was approved by the Regional Committee for Medical Research Ethics, Western Norway.

Other environmental chemicals. Three individuals (EF, LR and ÅS) were exposed, during three 1-week test periods, to environmental chemicals, with or without PHO, MOR and SUX allergens, available in Norway. For comparison liquorice raw material for sweet production (Æter & Essencefabriken, Stockholm, Sweden) was tested (Table 1). Four daily doses of liquorice sweets at a total amount of 256 g/week were taken during test period No. 1, and during test period No. 3 Fishermans Friends salmiak lozenges (Lofthouse of Fleetwood Ltd., Fleetwood, Lancashire, England) six times daily totalling 42 lozenges together with three times washing the hair with L'Oréal Professional Vitamino Color shampoo (L'Oréal Professional, Paris, France). As a reference four daily tablets of Dekadin menthol (Nycomed, Oslo, Norway), that does not contain the allergens in question, were taken during test period No. 2. Serum was collected directly before and after each exposure period to monitor any effect on levels of IgE and IgE antibodies to PHO, MOR and SUX.

Table 1. The degree of PHO, MOR and SUX inhibition of various household chemicals, including confectionary and hair shampoos, considered for the exposure studies. All products were bought in Norway. Liquorice raw material, used by the sweet industry, was also tested. The allergen content is expressed as capacity to inhibit the respective IgE system. The degree of inhibition is expressed in four grades: <10% –, 10–30% +, 30–60% ++ and >60% +++

Product	PHO	MOR	SUX	Exposure test
Decadin, solhatt	+	+	–	Used
Decadin, milk	–	–	+	
Decadin, menthol	–	–	–	
Liquorice, raw material	+++	+++	++	Used
Skipper, liquorice	+	++	–	
Kick, liquorice toffee	–	++	++	
Lacryl, lozenges	–	+	+	Used
Läkerol, liquorice	+	++	++	
Nox, liquorice	–	+	+	
Fisherman's friend, salmiak	++	+++	++	Used
Fisherman's friend, mandarine	–	–	–	Used
L'Oréal, vitalo	++	++	+++	
L'Oréal, vitamino	++	+++	+++	Used

PHO, pholcodine; MOR, morphine; SUX, suxamethonium.

Immunological analyses

IgE and IgE antibodies to PHO, MOR and SUX were analysed by ImmunoCAP[™] using PHO and MOR as described (2), glycine for evaluation of possible nonspecific binding, and commercially available SUX (c202) and other common allergens on ImmunoCAP, following the recommendations of the manufacturer. When measuring high concentrations of IgE (e.g. EF post-PHO) the serum samples were diluted in the diluent provided by the manufacturer. IgE activity of serum EF was subjected to inhibition with 10-fold serial dilutions in PBS of casein, ovalbumin, betalactoglobulin, succinylcholine, choline, PHO and cat dander from 10 mg/ml. Purified, monoclonal IgE [myeloma IgND (3)] was used as a reference.

IgE was also determined with Pharmacia CAP System FEIA (Pharmacia Diagnostics) and with an in-house sandwich-type ELISA, with a rabbit antihuman IgE coated on a microtitre-plate (Nunc AS, Roskilde, Denmark) and a secondary antibody of the same type, alkaline phosphatase conjugated (Sigma, St Louis, MO, USA). Fractions from gel filtration (see below) were screened for IgG and IgM by a similar in-house ELISA. Serum IgG, IgA, IgM and IgD analyses were kindly performed by the KSLAB, Karolinska University Hospital, Stockholm, Sweden.

Lymphocyte proliferation of peripheral blood mononuclear cells (PBMC) was assayed by incorporation of [³H]thymidine (4). PBMC were cultured in 96-well flat-bottomed plates (Falcon[®], Becton Dickinson, Franklin Lakes, NJ, USA) in RPMI 1640 (GIBCO[™], Invitrogen Corporation, Carlsbad, CA, USA) supplemented with 10% foetal calf serum (HyClone, Utah, USA), gentamycin (25 µg/ml), L-glutamine (2 nM), penicillin (100 IU/ml), streptomycin (100 µg/ml; all from GIBCO[™]) and 2-mercapto-ethanol (20 µM; Kebo-lab, Spånga, Sweden). The cells were stimulated with PHO, codeine and ethylmorpholine at dosages 0.01–100 µg/ml for 3 and 6 days. Stimulation index (SI) was calculated as a mean c.p.m. for antigen-stimulated PBMC divided by mean c.p.m. for PBMC cultured in medium alone. SI > 2.0 was considered as a positive proliferation response. As positive controls were added 1 µg/ml purified tuberculin protein derivative (Statens Seruminstitut, Copenhagen, Denmark) and 10 µg/ml tetanus toxoid (Statens Seruminstitut), evaluated after 3 days of incubation, and 5 µg/ml phytohaemagglutinin, after 6 days. Cell viability was determined by trypan blue exclusion.

Household chemical inhibition analyses

Inhibitions were made as previously described (2). Lozenges and sweets were bought in Norway and extracts 1/10 w/v in PBS were analysed for PHO, MOR and SUX allergenic activity by IgE antibody inhibition as determined by ImmunoCAP[™]. The results (Table 1) were expressed in percent of a PBS control for no inhibition. No significant inhibition, <10%, was expressed as –, 10–30% inhibition as +, 30–60% as ++ and >60% as +++.

Gel filtration

Serum was subjected to size exclusion chromatography (SEC) on a Superose 6 column HR 10/30 (Amersham Bioscience, UK), and the distribution of IgE, IgG and IgM was measured. Serum of EF from the IgE peak (day 56) was diluted 1/10 and the corresponding serum HE (day 42) 1/5 in PBS containing 0.02% NaN₃. A 100 µl aliquot of the samples was separated at 0.4 ml/min and 0.5 ml fractions were collected for analyses.

Results

Serological effects of exposure to PHO

Two individuals, EF, IgE-sensitized to PHO, MOR and SUX and HE, to PHO and MOR, were, during a first control week, taking codeine and noscapine, respectively. Neither of them developed any clinical symptoms or changes in serum levels of IgE or IgE antibodies to the three substances.

After 7 days with the PHO containing cough syrup EF experienced a severe pruritus, which disappeared within a few hours on oral antihistamine. The cough syrup was withdrawn and a blood sample showed a 60-fold increase of IgE (Fig. 1 and Table 2). IgE antibody to PHO, MOR and SUX showed a 60–85 times increase (Fig. 2A and Table 2). Similarly, HE developed on day 6 on his wrists mild, localized urticaria, which disappeared after oral antihistamine and did not make him stop taking the cough syrup. Serum drawn 24 h later showed a fourfold increase in IgE concentrations (Fig. 1 and Table 2) and 2 weeks later a 105-fold increase. The IgE antibody levels to PHO and MOR increased 95- and 77-fold, respectively, and IgE antibodies to SUX from <0.1–5.6 kU_A/l (Fig. 2B and Table 2).

In contrast, the IgE concentrations of the two nonsensitized controls, HÖ and TH, did not change during either noscapine or PHO exposure and no IgE antibodies appeared (Fig. 1 and Table 2).

When IgE levels were followed during the next month's different patterns in IgE decrease was seen (Fig. 1). In EF during the first 10 weeks IgE decreased with a $T_{1/2}$ of approximately 40 days followed by 16 weeks (summer time) with no significant decrease, a return to a decrease similar to the initial one and then again a stable four period (Christmas time). In contrast, IgE in samples from HE started by dropping drastically, $T_{1/2}$ of approximately 10 days, but started to level out 6–8 weeks after exposure.

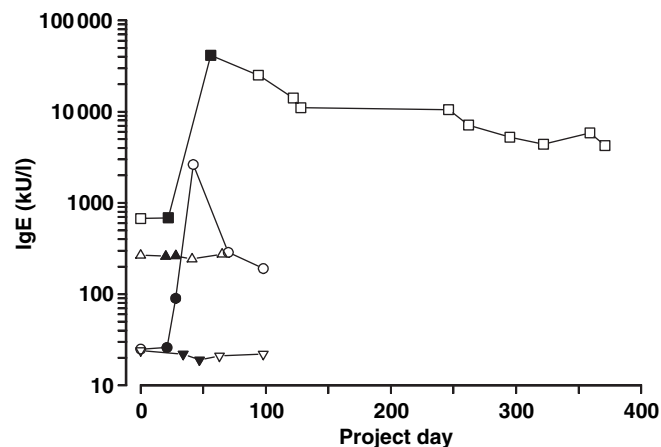


Figure 1. Serum levels of IgE (kU/l) of person EF (□), HE (○), HÖ (△) and TH (▽) before and after oral intake (between filled symbol) of cough syrup containing PHO.

Table 2. IgE (kU/l) and IgE antibody (kU_A/l) to PHO, MOR and SUX in the four persons in the cough syrup exposure trial. Glycine (kU_A/l) refers to background activity

Person	Sample type	Day	IgE	PHO	MOR	SUX	Glycine
EF	Pre	0	675	4.3	6.7	1.4	<0.1
	After placebo	22	686	4.0	6.7	1.5	<0.1
	After active	56	41 480	338	417	119	3.3
	Post	94	25 120	210	318	91.2	2.5
	Post	122	14 130	206	276	73.0	1.7
	Post	128	11 030	167	184	35.0	1.4
HE	Pre	0	25	1.1	1.0	<0.1	<0.1
	After placebo	21	26	1.1	1.1	<0.1	<0.1
	After active	28	90	1.1	2.8	<0.1	<0.1
	Post	42	2640	62.1	62.4	5.6	<0.1
	Post	70	287	5.6	6.7	0.4	<0.1
	Post	128	268	<0.1	<0.1	<0.1	<0.1
HÖ	Pre	0	268	<0.1	<0.1	<0.1	<0.1
	After placebo	20	260	<0.1	<0.1	<0.1	<0.1
	After active	28	263	<0.1	<0.1	<0.1	<0.1
	Post	41	243	<0.1	<0.1	<0.1	<0.1
	Post	69	274	<0.1	<0.1	<0.1	<0.1
	Post	98	22	<0.1	<0.1	<0.1	<0.1
TH	Pre	0	24	<0.1	<0.1	<0.1	<0.1
	After placebo	34	22	<0.1	<0.1	<0.1	<0.1
	After active	47	19	<0.1	<0.1	<0.1	<0.1
	Post	63	21	<0.1	<0.1	<0.1	<0.1
	Post	98	22	<0.1	<0.1	<0.1	<0.1
	Post	98	22	<0.1	<0.1	<0.1	<0.1

PHO, pholcodine; MOR, morphine; SUX, suxamethonium.

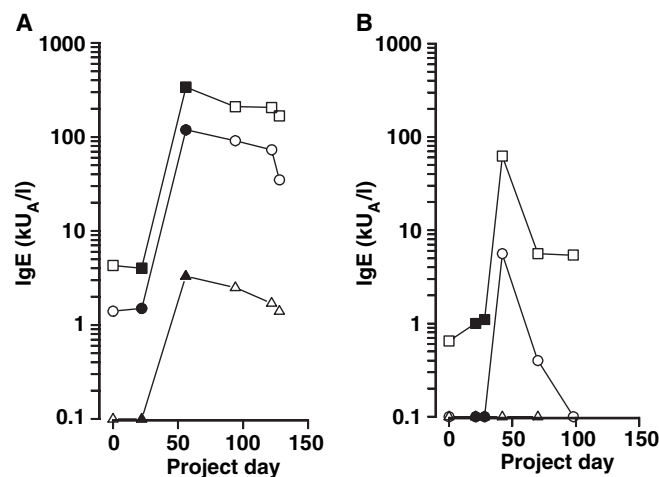


Figure 2. Levels of IgE antibodies (kU_A/l) to PHO (□) and SUX (○) and background control glycine (△) in serum samples of EF (A) and HE (B) taken before and after oral intake (between filled symbols) of cough syrup containing PHO.

No changes of IgG, IgM, IgA or IgD serum levels were seen.

Characterization of PHO-stimulated IgE

Serum from EF, taken on project day 56, was tested for IgE antibodies to cat (e1), *D. pteronyssinus* (d1), ovalbumin (f232), timothy (g6) and casein (f78) and high levels, 3.1–5.4 kU_A/l, were found. Before PHO exposure

a weak reaction corresponding to 0.5 kU_A/l to e1 was found while no reaction, <0.2 kU_A/l, was detected to the other allergens. Serum of HE taken on project day 42 was weakly positive, 0.5 kU_A/l, to timothy. IgG antibodies in EF and HE to PHO, MOR and SUX increased two to fourfold, whereas IgG antibodies to g6 and e1 were unaffected. Cross-inhibition of serum EF was performed on one hand with casein, ovalbumin, betalactoglobulin and cat allergen and on the other with PHO. PHO, but not ovalbumin, betalactoglobulin or casein, gave a dose/response inhibition of its homologous system and neither of the three inhibited PHO or vice versa. PHO did not block the IgE binding to cat ImmunoCAP and cat did not interfere in the PHO system. However, inhibition of the cat homologue system gave inconsistent results and, in contrast to the other allergens, SUX at lower dilutions, i.e. 1/10–1/100, gave an inhibition-like interference.

No increased binding of IgE, i.e. <0.2 kU_A/l, was found for the tested ImmunoCAPTM allergens or glycine as background ImmunoCAP using purified, monoclonal IgE at concentrations of 10 000–80 000 kU/l. Post-PHO samples from EF, but not HE, gave 1–3 kU_A/l against glycine at comparable IgE levels (Table 2). Similar results were obtained in Pharmacia CAP System FEIA and ELISA.

On SEC, IgE from EF and HE, eluted after IgM and just before IgG (Fig. 3), as expected of monomeric IgE.

Cellular responses to PHO

Lymphocyte proliferation was performed on a sample of EF taken on project day 262. Upon stimulation with 0.01–100 µg/ml of PHO, codeine or etylmorpholine a dose/response incorporation of thymidine was obtained after

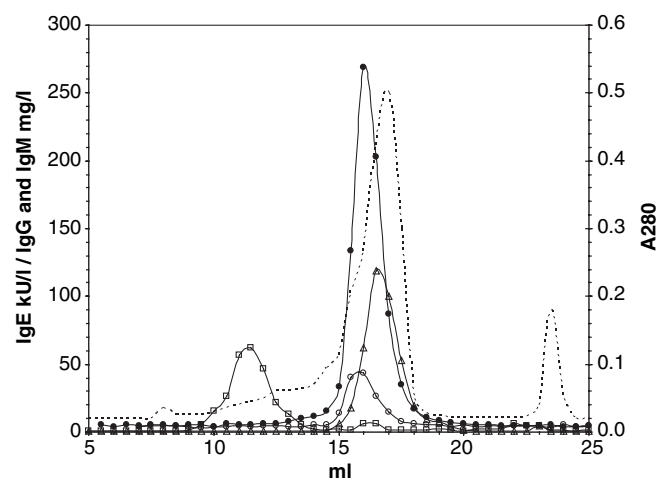


Figure 3. Size exclusion chromatography (SEC) on Superose 6 (A₂₈₀ ---) of appropriately diluted serum EF and HE, after the PHO-intake, comparing distribution of IgE of EF (●) and HE (○) with that of IgG (△) and IgM (□) of HE. The values of IgM were multiplied by 10 before being plotted to make the peak easier to see.

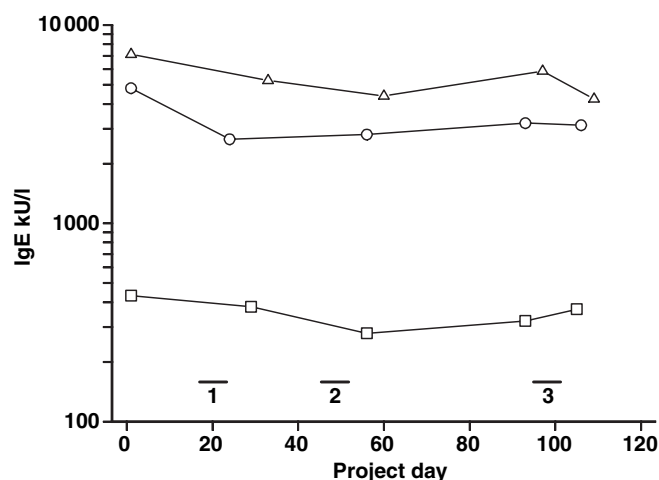


Figure 4. IgE values in samples from EF (△), LR (○) and ÅS (□) taken before and after the three 1-week household chemical exposure sessions (marked 1, 2 and 3).

6 days with PHO with a maximum of five times the response of the negative control. No proliferation was detected with codeine and etylmorpholine. One experiment with lymphocytes from a nonsensitized individual was found negative.

Exposure to household chemicals

Three PHO sensitized individuals (EF, LR and ÅS) were exposed to household chemicals selected for containing or lacking PHO, MOR and SUX allergenic epitopes (Table 1). In neither case any consistent effect on the concentrations of IgE (Fig. 4 and Table 3) and IgE antibodies to PHO, MOR or SUX could be seen (Table 3). However, during the household chemical exposure period, just over 100 days, the levels of IgE and IgE antibodies were rather stable.

Discussion

The allergenic epitope thought to be responsible for the allergic anaphylaxis seen after administration of NMBA during anaesthesia is a quaternary ammonium ion, QAI (5). It has been recommended that individuals at risk should be identified from having IgE antibodies to MOR, which has QAI (6). However, since MOR is monovalent for the QAI allergen epitope it cannot be used in skin tests or basophil challenge tests (7).

Attempting to explain the great differences in NMBA-related anaphylaxis in Norway and Sweden, screening for IgE antibodies to MOR and SUX was performed. Significant differences were found; among probably allergic individuals 30/301 in Norway but 0/300 in Sweden, were IgE-sensitized to MOR (2). However, only 3.7% had IgE antibodies to SUX, indicating allergenic differences between SUX and MOR. Indeed it was found

Table 3. Effects on concentrations of IgE (kU/l) and IgE antibodies (kU_A/l) to PHO, MOR and SUX of 1 week of exposure to selected household chemicals, i.e. eating some sweets with (Kick liquorice toffee and Nox liquorice) and without (Decadin menthol) and washing hair in shampoo (L'Oreal Professional Vitamino) with such allergenic epitopes

Chemical	Person	IgE		PHO		MOR		SUX	
		Before	After	Before	After	Before	After	Before	After
Decadin menthol	ÅS	430	380	1.0	0.9	2.1	2.2	<0.35	<0.35
	LR	4810	2660	226	192	96.7	78.9	0.5	0.4
	EF	7130*	5260	80.6	43.3	166	116	22.8	10.7
Liquorice	ÅS	380†	280	0.9†	1.0	2.2†	2.3	<0.35†	<0.35
	LR	2660†	2810	192†	181	78.9†	67.3	0.4†	0.5
	EF	5260†	4390	43.3†	44.5	116†	119	10.7†	10.6
FF Salmiak and L'Oreal shampoo	ÅS	320	370	1.0	1.0	1.9	1.8	<0.35	<0.35
	LR	3200	3130	174	173	82.5	69.9	0.5	0.5
	EF	5860	4240	48.4	17.4	130	56.8	11.3	8.2

*Sample 'before' was drawn on day 262 after cough syrup challenge IgE peak.

†From sample after previous provocation period.

PHO, pholcodine; MOR, morphine; SUX, suxamethonium.

that MOR, in addition to QAI, carries a unique allergenic epitope.

Possible reasons for this difference in IgE-sensitization to MOR and SUX between Norway and Sweden were sought among household chemicals. The most likely candidates were cough syrups containing PHO (2). Such drugs were only available in Norway and then as OTC. The suspicion was supported by reports from WHO (8) indicating that, on a national basis, there appears to be a relation between per capita consumption of PHO and prevalence of anaphylaxis to NMBA. Examples of countries with high consumption and high prevalence are Australia, France, Ireland and Norway while low figures for both parameters are reported from Denmark, Germany, The Netherlands, Sweden and USA.

Studies showed that PHO contained both the QAI and the MOR-specific allergenic epitopes (2) and it was found that two thirds of sera from patients that had experienced an anaphylaxis to NMBA had IgE antibodies specific to the PHO/MOR epitope compared to one third to QAI (2).

Serum from PHO/MOR/SUX sensitized individuals collected during the last 2–3 years showed remarkable fluctuations in IgE and IgE antibody concentrations. To investigate if such changes could be due to periodic intake of a PHO containing cough medicine, it was decided to expose two IgE-sensitized individuals. Tuxi cough mixture was chosen since it contains PHO and is consumed in great quantities in Norway; according to WHO statistics, during 1994–1998, 2773 doses per million inhabitants (9). Interestingly, after taking the drug for 6–7 days EF developed severe, general pruritus and HE localized urticaria.

The cough syrup had a remarkable IgE-stimulating potency in sensitized individuals. Serum from EF and HE obtained closely after taking the drug showed a 60–105-fold increase of IgE. In EF the IgE concentrations decreased slowly with a $T_{1/2}$ of 40 days while in HE it

dropped more readily, $T_{1/2}$ about 10 days. No significant changes were seen of the other four immunoglobulins. Like IgE, the levels of IgE antibodies to PHO, MOR and SUX increased dramatically, 30–80-fold. These increases should be compared to the two to threefold raise observed during a pollen season (10).

It is difficult to explain the immunological mechanisms behind the booster effect, but it is most likely linked to PHO. Very little effect on IgE was seen after the week with codeine, which seems to carry the two allergenic epitopes, and noscapine, which only has the QAI. The lymphocytes of EF, when stimulated with PHO in the lymphocyte proliferation test, showed a fivefold response, which is quite low compared to the 60-fold increase in serum IgE concentrations. No stimulation was seen by codeine and ethylmorpholine.

It is possible that PHO has a mitogen-like effect restricted to IgE synthesis in a way similar to what has been found in helminth infestations (11), certain viral infections (12) and after *Staphylococcus aureus* infection (13). In the graft vs host disease after bone marrow transplantation a very rapid increase restricted to IgE is seen but the effect is not restricted to individuals with any known IgE-sensitization (14). It is not known if the rapid fluctuations in serum IgE levels could have any clinical consequences but they could be of concern for efficacy of anti-IgE treatment for allergy (15). The mechanisms of the PHO immune stimulation deserve further studies.

During the summer and Christmas periods the IgE level of EF did not change, most likely due to some stimulation from general household chemicals, since no cough syrups were taken. Although, in the exposure studies using a few selected sweets and other environmental chemicals containing the allergens no impressive stimulatory effects were seen, the serum IgE levels were remarkably stable during the more than 3 months the three individuals were monitored.

The very similar degree of increase of IgE and IgE antibodies to PHO, MOR and SUX in EF indicate a polyclonal booster effect of PHO. The hypothesis was supported by the finding of quite high, 3–5 kU_A/l and values in ImmunoCAP™ to some classical allergens. Similar effects were observed in HE. However, this antibody like binding to the ImmunoCAP™ could not be inhibited with the corresponding allergen. In contrast, the reaction to PHO was inhibited by PHO in a dose/response way. These findings indicate that the IgE response to PHO, MOR and SUX is that of a classical antibody, a conclusion supported by the positive lymphocyte proliferation test to PHO, which contains both QAI and the MOR/PHO specific allergens.

The negative inhibition results of the classical allergens and the binding corresponding to 1–3 kU_A/l, to 'empty', i.e. glycine, ImmunoCAP™, indicate a nonspecific binding of IgE. The results of EF to cat, both before and after PHO intake, are difficult to understand. However, purified, monoclonal IgE (3), at levels 5–10 times of those induced by PHO, did not give any significant nonspecific binding, i.e. ImmunoCAP values higher than 0.2 kU_A/l.

One possible explanation for the high nonspecific binding could be the presence in serum of immune complexes containing IgE or both IgE and IgG. It is well known that complexed IgG, can give background problems in immunoassays. However, the IgE involved in the nonspecific binding was found to be monomeric. Thus the immunological and immunochemical nature of the IgE appearing after PHO stimulation deserves to be further studied.

It seems from this study that if an individual, IgE-sensitized to the PHO/MOR allergenic epitope, is

exposed to even small amounts of cough syrups containing PHO, the IgE system is very strongly stimulated. This boosting includes IgE antibodies to the QAI-like epitopes. Thus, it is possible that such cough syrups, by sensitizing and boosting, could put people at risk for developing an allergic anaphylaxis to NMBA. In addition, if the sensitized individual is a blood donor, transfusion of his blood and plasma will passively sensitize the recipient (16) who then might become at risk for an NMBA-induced anaphylaxis.

In conclusion, easily accessible cough syrups containing PHO seem capable to sensitize, and certainly strongly booster already sensitized, individuals to produce IgE antibodies to allergenic epitopes like QAI thought to be responsible for allergic anaphylaxis to NMBA. In addition, serum IgE levels increased dramatically. To document to what extent the finding that cough syrups containing PHO give a high booster effect of IgE and IgE antibody synthesis in sensitized individuals a controlled trial is presently carried out. Further studies should be performed on national basis confirming the relation between prevalence's of IgE antibodies to PHO, MOR and SUX and prevalence of allergic anaphylaxis to NMBA.

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