

Prick testing with chemicals in the diagnosis of occupational contact urticaria and respiratory diseases

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Summary

Background. Little is known about the use of prick tests with chemicals in diagnosing occupational diseases.

Objective. To evaluate the use of prick tests in the diagnosis of occupational contact urticaria, asthma and rhinitis caused by chemicals (undertaken at the Finnish Institute of Occupational Health).

Material and methods. We retrospectively reviewed the patient and test files for the period 1 January 1991 to 31 May 2011. Prick tests were performed with chemical solutions and human serum albumin (HSA)–chemical conjugates.

Results. Positive prick test reactions to isocyanate–HSA conjugates were associated with isocyanate-specific IgE in all 20 patients, and 17 patients had a relevant occupational disease. Positive reactions to chloramine-T–HSA conjugates in 10 patients also indicated the presence of specific IgE, although occupational diseases were not always diagnosed. Eleven of 17 patients with positive reactions to persulfate solutions were diagnosed with an occupational disease. Methacrylates, colophonium-related substances, amine hardeners, ethanolamines, glutaraldehyde, glyoxal, pyrocatechol and ammonium thioglycolate did not elicit any relevant prick test reactions. No generalized reactions were detected.

Conclusion. Prick tests can be safely used for diagnosing contact urticaria, asthma and rhinitis caused by isocyanates, chloramine-T, persulfates, and chlorhexidine, but the results should be carefully interpreted and related to clinical symptoms and other diagnostic tests.

Key words: chloramine-T; chlorhexidine; epoxy resin; human serum albumin conjugates; isocyanates; persulfates; specific IgE.

Occupational contact urticaria and respiratory diseases caused by chemicals are rare as compared with allergic contact dermatitis. The mechanisms by which chemicals cause the immediate hypersensitivity diseases are mainly unknown (1). An IgE-mediated mechanism is considered to be probable for at least some chemicals (2),

and prick testing has therefore been tried as a diagnostic tool in screening these patients (3). Prick testing is fast, and enables the testing of several chemicals simultaneously. Commercial prick test substances are not available for chemicals, and neither are diagnostic guidelines. Examples of testing procedures can be found in the literature, but usually describe only single cases or small series of cases. Commercial assays for the determination of specific IgE have been developed for some chemicals.

Human serum albumin (HSA) conjugates of chemicals have been used for the determination of specific IgE at the Finnish Institute of Occupational Health (FIOH) since the 1980s. This led to an interest in using HSA conjugates

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for prick testing. Patients with suspected occupational diseases caused by chemicals have been routinely prick tested with chemicals at the FIOH for over two decades, but the testing methods have varied over the years.

A positive prick test result does not by itself indicate an allergic disease. At the FIOH, occupational disease diagnoses are based on objective findings in additional tests, for example provocation tests, combined with work-related symptoms.

The aim of this study was to evaluate the relevance and usefulness of prick testing for diagnosing occupational contact urticaria, asthma and rhinitis caused by chemicals. We have shown the relevance of prick testing in the diagnosis of contact urticaria caused by acid anhydrides in an earlier report (4), and thus will not cover them in this report.

Materials and Methods

We retrospectively reviewed the FIOH's patient and test files for the period of 1 January 1991 to 31 May 2011, to find all patients with at least one positive prick test result in the prick tests performed routinely with chemicals. From the medical records of the patients, we collected data on exposure, the results of clinical examinations and immunological tests, and diagnosed occupational diseases. Data on the individual chemicals in the prick tests and their CAS numbers, the types of test substances, the number of patients tested and the number of positive reactions are shown in Table 1.

Many chemicals (e.g. acid anhydrides, diisocyanates, and epoxy resin) were tested as hapten conjugates of the chemical and HSA. The conjugation between, for example, acid anhydrides and HSA was carried out essentially as described by Howe et al. (5). The diisocyanate–HSA conjugates were prepared according to Wass and Belin (6).

Hapten chemicals dissolved in a suitable solvent were allowed to react with 1% HSA (ALBUMIN SPR 200 mg/ml; Finnish Red Cross Blood Transfusion Service, Finland) in a mild alkaline buffer and ice bath for ~1 hr. Solvents and buffers were selected according to the haptens.

After filtration through filter paper, the hapten–HSA conjugate was concentrated to give a solution containing 2% HSA, and the buffer was changed to 'coca' solution (0.5% sodium chloride, 0.3% sodium hydrogen carbonate, and 0.4% phenol) by ultrafiltration through an Ultracel 10-kDa membrane (Millipore, Billerica, MA, USA). Control HSA solution was prepared in the same manner without the haptens.

Hapten–HSA solution (2.5 ml) was passed through a Millex-GV filter with a 0.22- μ m membrane (MerckMillipore Ltd, Tullagreen, Carrigtwohill, Co. Cork, Ireland) into a sterile vial containing 2.5 ml of glycerol, to give a final HSA concentration of 10 mg/ml (1%).

For some chemicals, solutions with water or coca/glycerine (0.5% NaCl, 0.275% NaHCO₃, 0.4% phenol, and glycerol 1:1) as a vehicle were used parallel with or instead of the HSA conjugates. A prick test reaction was considered to be positive if the wheal caused by the test reagent had a minimum diameter of 3 mm and was at least half the size of the positive histamine control wheal (histamine hydrochloride 10 mg/ml) in the absence of a reaction to the negative control.

For the determination of specific IgE, several different commercial methods and in-house radio-allergosorbent test methods were used during the study period. We currently primarily use ImmunoCAP 100 (Phadia AB, Uppsala, Sweden). Specific IgE was determined for diisocyanates, epoxy resin, chloramine-T, formaldehyde, chlorhexidine, and colophonium.

Open application (skin provocation) was performed on patients with suspected contact urticaria in accordance with the methods described in our previous report (4). A positive open application result was not considered to be necessary for diagnosing contact urticaria if the clinical symptoms were typical and sensitization had been shown by other test methods.

Specific inhalation challenge was the principal method used to confirm the diagnosis of occupational asthma and rhinitis; in addition, we used serial peak flow monitoring. Placebo-controlled challenges were performed in challenge chambers as work simulation or nebulization of the occupational agent in the air. These included a 24-hr follow-up for each agent. The test was considered to be positive for occupational asthma if the forced expiratory volume in 1 second and or peak flow fell by ≥ 15 –20% of the prechallenge value without significant changes in the control challenge. The degree of rhinorrhoea and nasal blockage was scored with anterior rhinoscopy (7). A significant score change without a significant change following the control challenge was considered to be positive for occupational rhinitis; nasal secretion of ≥ 200 mg supported the positive reaction.

A few nasal provocation tests were performed on patients with suspected occupational rhinitis, according to the methods described by Airaksinen et al. (8). The usefulness of nasal provocation tests with chemicals is limited by the irritant effects of many chemicals.

Table 1. Routinely tested chemicals 1991–2011: groups of chemicals and their individual allergens, types of test substances, number of patients tested, and number of prick test-positive patients

Groups of chemicals	Individual chemicals of the group	Type of test substance	Number of patients tested	Number of prick test-positive patients (percentage of patients tested)
Isocyanates	HDI (CAS no. 822-06-0) MDI (CAS no. 101-68-8) TDI (mixture of 2,4-TDI and 2,6-TDI; CAS nos. 584-84-9 and 91-08-7)	Hapten–HSA conjugates	1320	20 (1.5)
Chloramine-T	Chloramine-T (CAS no. 127-65-1)	(a) 1% solution (in coca/glycerine 1998–2001 or aq. since 2001) (b) Hapten–HSA conjugate (1998–2010)	597 HSA conjugate 580	1% solution: 11 (1.8) HSA conjugate: 10 (1.7)
Epoxy resin	Diglycidyl ether of bisphenol A (CAS no. 1675-54-3)	Hapten–HSA conjugate	1268	19 (1.5)
Amine hardeners	EDA (CAS no. 107-15-3) DETA (CAS no. 111-40-0) TETA (CAS no. 112-24-3) MDA (CAS no. 101-77-9) IPDA (CAS no. 2855-13-2) tris-DMP (CAS no. 90-72-2) MXDA (CAS no. 1477-55-0) TMD (CAS no. 25513-64-8)	(a) Hapten–HSA conjugates (b) 1% solution (in coca/glycerine)	796	25 (3.1)
Persulfates	Ammonium persulfate (CAS no. 7727-54-0) Potassium persulfate (CAS no. 7727-21-1)	2% aq.	Ammonium persulfate 803 Potassium persulfate 806	17 (2.1)
Other hairdressing chemicals	PPD (CAS no. 106-50-3)	Hapten–HSA conjugate	166	1 (0.6%)
	Pyrocatechol (CAS no. 120-80-9)	Hapten–HSA conjugate	112	0
	Ammonium thioglycolate (CAS no. 5421-46-5; until 2006)	10% aq.	191	0
Chlorhexidine	Chlorhexidine digluconate (CAS no. 18472-51-0; since 1998)	0.5% aq.	337	1 (0.3)
Aziridines	PFA (CAS no. 64265-57-2)	(a) Hapten–HSA conjugate (b) 0.1% and 1% aq.	46	4 (8.7)
Methacrylates	2-HEMA (CAS no. 868-77-9) MMA (CAS no. 80-62-6) PEGDMA (CAS no. 25852-47-5; until 1995)	Hapten–HSA conjugate	1158 PEGDMA 243	1 (0.08)
Ethanolamines	Ethanolamine (CAS no. 141-43-5) Diethanolamine (CAS no. 111-42-2) Triethanolamine (CAS no. 3077-12-1)	(a) Hapten–HSA conjugate (b) 1% solution (in coca/glycerine)	386	0
Aldehydes	Formaldehyde (CAS no. 50-00-0)	(a) 1% solution (in aq. 1991–2001 and in coca/glycerine since 2001) (b) Hapten–HSA conjugate (since 2001)	2703 HSA conjugate 1053	21 (0.78)
	Glutaraldehyde (CAS no. 11-30-8)	(a) Hapten–HSA conjugate (b) 1% solution (in coca/glycerine)	1214	2 (0.16)
	Glyoxal (CAS no. 107-22-2)	(a) Hapten–HSA conjugate (b) 1% solution (in coca/glycerine)	1051	0
Colophonium-related substances	Colophonium (CAS no. 8050-09-7) Tall oil rosin (CAS no. 8052-10-6) Abietic acid (CAS no. 514-10-3; since 1999)	(a) Hapten–HSA conjugate (b) 10 and 100 mg/ml extracts (not abietic acid)	1553 Abietic acid 608	2 (0.13)

DETA, diethylenetriamine; EDA, ethylenediamine; 2-HEMA, 2-hydroxyethyl methacrylate; HDI, hexamethylene diisocyanate; HSA, human serum albumin; IPDA, isophorone diamine; MDA, diaminodiphenylmethane; MDI, diphenylmethane diisocyanate; MMA, methyl methacrylate; MXDA, *m*-xylylenediamine; PEGDMA, polyethyleneglycol dimethacrylate; PFA, polyfunctional aziridine; PPD, *p*-phenylenediamine; TDI, toluene diisocyanate; TETA, triethylene tetramine; TMD, trimethylhexamethylene diamine; tris-DMP, 2,4,6-tris-dimethylaminomethylphenol.

Results

Table 1 shows the total numbers of patients who reacted to each chemical group. No strong or generalized prick test reactions requiring special medical attention were detected. Table 2 shows 20 patients (1.5% of 1320 patients tested) with a positive prick test reaction to at least one diisocyanate. The patients were exposed by using polyurethane paints, coatings, and glues, and during the manufacture of polyurethane products. Table 3 shows 11 patients (1.8% of 597 tested patients) who reacted to chloramine-T. All of the patients were healthcare workers who had used cleaning substances and disinfectants containing chloramine-T.

Epoxy resins

Positive prick test reactions to the HSA conjugate of diglycidylether of bisphenol A (DGEBA) were seen in 19 (1.5%) of 1268 patients (Table 4). The most common fields of work were the manufacture of electrical machines and the use of epoxy paints and coatings. A patient with both occupational asthma and contact dermatitis caused by epoxy resin has been described in an earlier FIOH report (10). Only 1 other patient with occupational asthma caused by epoxy resins was diagnosed in the group. On the other hand, 10 of the patients were diagnosed with an IgE-mediated occupational disease (asthma, rhinitis, or contact urticaria) caused by an organic acid anhydride used as a curing agent in the epoxy resin system.

Amine hardeners for epoxy resins

Eight different amine hardeners for epoxy resins were tested, and 25 patients of 796 tested had prick test reactions of 3–5 mm to some amine hardener, most commonly to isophorone diamine (11 patients; 1.1%) and trimethylhexamethylene diamine (5 patients; 0.6%). The reactions were only seen with coca/glycerine solutions, and not with the HSA conjugates. All reactions were smaller than the histamine reaction, and no occupational disease caused by amine hardeners was diagnosed in these patients.

Persulfates and other hairdressing chemicals

We found 17 patients (2.1% of 806 tested) with positive prick test reactions to persulfates. Fifteen of these were hairdressers (Table 5).

One positive prick test reaction to *p*-phenylenediamine (PPD) occurred in a hairdresser with contact urticaria and anaphylactic symptoms (11), but there were no positive reactions to ammonium thioglycolate or pyrocatechol.

Chlorhexidine

Prick tests with chlorhexidine digluconate were performed 337 times, mainly on healthcare workers. Occupational contact urticaria caused by chlorhexidine in handwash and mouthwash was diagnosed in a dental nurse. Her 6-mm reaction was the only positive reaction to chlorhexidine in our study population, although she showed no chlorhexidine-specific IgE. Two 3-mm reactions were not considered to be clinically significant, as they were less than half the size of the histamine reaction and the patients' symptoms were not clearly associated with chlorhexidine.

Aziridine

The prick test with polyfunctional aziridine (PFA) hardener performed on 46 patients exposed to aziridine in paint and coatings gave a clearly positive result in 1 patient with occupational contact urticaria: 1% aq. elicited a histamine-sized 6-mm reaction, 0.1% aq. elicited a 3-mm reaction, and the PFA–HSA solution elicited a 3-mm reaction. The case is described in an earlier report (12). Three small positive 3-mm reactions also occurred. One of the patients was diagnosed with occupational asthma caused by an aziridine-containing paint hardener.

Methacrylates

HSA conjugates were used in the prick testing of dental personnel and other workers exposed to methacrylates. One patient (of 1158 tested) had 3-mm reactions to all three methacrylates tested, but no occupational disease was diagnosed.

Ethanolamines

The ethanolamines tested in 386 patients, mainly metal workers and cleaning personnel, elicited no positive reactions.

Aldehydes

During the study period, 21 patients of 2703 (0.78%) had prick test reactions to formaldehyde that fulfilled the criteria for a positive test result. Exposure to formaldehyde occurred in a wide range of occupational settings. The prick test reactions were 3–6 mm in size, and no reactions larger than the positive control wheal were noted. In addition, 15 patients had a prick test reaction of 3 mm, but this was less than half the size of the control wheal. Formaldehyde-specific IgE was determined in 20 of these

Table 2. Patients with positive prick test reactions to isocyanates: exposure, prick test reactions, specific IgE, isocyanate-related diagnoses, and reactions in specific inhalation challenges and open skin application

Patient	Exposure	HDI		MDI		TDI		Isocyanate-related diagnosis	Specific inhalation challenge (SIC)		Ref.
		Prick (mm)	IgE (kU/l)	Prick (mm)	IgE (kU/l)	Prick (mm)	IgE (kU/l)		Open skin application	Open skin application	
1	HDI	4	3.13	3	1.34	3	1.75	–	SIC: HDI hardener: negative	–	–
2	HDI	4	6.92	2	0.57	3	0.81	Asthma	SIC: HDI hardener: asthmatic reaction	–	–
3	HDI	4	2.7	0	1.1	0	0.6	Asthma	SIC: HDI hardener: asthmatic reaction	–	–
4	HDI	5	4.6	0	1.5	0	1.9	Contact urticaria	SIC: HDI hardener: negative	–	–
									Open skin application with HDI hardener 1% negative		
5	HDI	3	7.5	0	1.4	0	1.4	Rhinitis	SIC: HDI hardener: rhinitis reaction	–	–
6	HDI	4	10.1	3	8.0	3	6.6	Asthma	SIC: HDI hardener: asthmatic reaction	–	–
7	HDI	4	6.2	0	ND	0	ND	Asthma, rhinitis	SIC: HDI hardener: asthmatic reaction	–	–
8	MDI (HDI)	8	4.15	6	7.09	7	ND	Asthma, rhinitis	ND	–	–
9	MDI	4	1.9	0	0.9	4	1.6	Rhinitis	ND	–	–
10	MDI	4	ND	6	7.6	4	ND	Contact urticaria	SIC: MDI: negative	–	–
									Open skin application with MDI–HSA conjugate positive		
11	MDI	0	0.72	4	1.29	2	0.84	Asthma, contact urticaria	ND	(9)	–
12	MDI	5	NT	5	2.9	5	ND	Asthma	SIC: MDI: asthmatic reaction	–	–
13	MDI	3	1.3	4	0.8	4	0.6	–	SIC: MDI: negative	–	–
14	MDI	4	ND	5	1.9	5	ND	Asthma, rhinitis	SIC: MDI: asthmatic reaction	–	–
15	MDI	0	ND	3	1.4	0	ND	Asthma	SIC: MDI: asthmatic reaction	–	–
16	MDI	0	ND	3	3.5	0	ND	Asthma	SIC: MDI: asthmatic reaction	–	–
17	MDI	2	ND	4	1.8	0	ND	Asthma, rhinitis	SIC: MDI: asthmatic and rhinitis reaction	–	–
18	MDI	2	ND	6	1.2	0	ND	Asthma	SIC: MDI: asthmatic reaction	–	–
19	MDI, TDI	6	8.0	8	17.5	4	12.0	Asthma	SIC: MDI: asthmatic reaction	–	–
20	TDI	3	2.0	3	1.1	3	2.1	–	ND	–	–

HDI, hexamethylene diisocyanate; MDI, diphenylmethane diisocyanate; ND, not determined; TDI, toluene diisocyanate.

Table 3. Patients with positive prick test reactions to chloramine-T: prick test reactions, results of specific IgE determinations, chloramine-T-related diagnoses, and results of specific inhalation challenge

Patient	Prick (mm)		IgE (kU/l)	Chloramine-T-related diagnosis	Specific inhalation challenge with chloramine T-containing detergent
	HSA conjugate	Aq. solution 1%			
1	12ps	9	0.59	–	Negative [†]
2	15ps	7ps	2.55	–	Negative
3	11ps	11ps	16	Contact urticaria	NT
4	6	9	0.8	–	Negative
5	9ps	NT	3.3	Rhinitis	Rhinitis reaction
6	7	NT	0.8	Contact urticaria	NT
7	11	NT	1.4	Asthma, rhinitis	Asthmatic and rhinitis reaction
8	9	NT	1.3	–	Negative
9	7	NT	5.2	–	NT
10	9	NT	5.6	–	Negative
11	3*	6	0	Contact urticaria	Negative (open application test positive in a local hospital)
12	0	3	0	–	Negative
13	0	3	<0.35	–	NT
14	0	3	<0.35	–	NT
15	NT	4	0	–	NT
16	1	3	<0.3	–	Negative

HSA, human serum albumin; NT, not tested; ps, pseudopodia.

*Less than 50% of the histamine reaction.

†Two repeated challenges.

patients, without positive results. Three cases of occupational asthma caused by formaldehyde were diagnosed in this group.

Only two reactions to glutaraldehyde (0.16% of 1214 patients) that met the criteria for a positive reaction were noted in the patients tested. Neither of these dentistry workers was diagnosed with an occupational disease caused by glutaraldehyde. No positive prick test reactions to glyoxal were found in the present study population.

Colophonium and related substances (Table 1)

Two patients working in the electronics industry (0.13% of 1553 tested) had 3–4-mm positive reactions to the test substances of this group, but neither of them had colophonium-specific IgE or was diagnosed with an occupational disease caused by colophonium.

Discussion

In Finland, dermatologists have a long tradition of working together with respiratory and ENT physicians and performing prick tests for their patients. Concomitant contact urticaria and respiratory diseases are common in occupational settings. Chemical-induced contact urticaria is rare, but might also be underdiagnosed, as attention is mainly focused on diagnosing possible occupational asthma. The symptoms of contact urticaria are

often mild, limited to areas of skin contact, and of short duration, and people rarely actively report them to their physician. If patients with a chemical-induced respiratory disease are asked specific questions relating to contact urticaria, the answers are quite often affirmative, and lead to the diagnosis of contact urticaria. Dermatologists experienced in contact allergy have experience in patch testing patients' own substances that can also be applied to performing prick tests in their patients.

Isocyanates

Isocyanates may induce IgE-mediated sensitization, but the relevance of immediate-type allergy is a matter of debate, as specific IgE cannot be determined in a majority of isocyanate asthma cases (13, 14). All of our 20 prick test-positive patients showed isocyanate-specific IgE, and the great majority of them were diagnosed with a relevant occupational disease: asthma, rhinitis, and/or contact urticaria. Concomitant prick test reactions to several isocyanates were quite common, but the largest prick test reaction was usually provoked by the isocyanate to which the patient was exposed, and was associated with the highest level of specific IgE. In 9 cases, however, patients only reacted to the isocyanate to which they were exposed, and not to the two other compounds. Specific IgE levels showed less specificity, as all measured values indicated sensitization irrespective of exposure.

Table 4. Patients with positive prick test reactions to diglycidylether of bisphenol A (DGEBA) epoxy resin: prick test reactions, DGEBA-specific IgE, DGEBA-related diagnoses, and results of specific inhalation challenge

Patient	Prick test (DGEBA–HSA conjugate) (mm)	Specific IgE (kU/l)	DGEBA-related diagnosis	Specific inhalation challenge	Ref.
1	3	ND	Asthma	Epoxy resin: asthmatic reaction	–
2	4	20	Asthma (ACD)	Epoxy resin (coating): asthmatic reaction	(10)
3	3	1.6	ACD	Epoxy paint: negative	–
4	5	1.1	ACD	NT	–
5	6	11	–	NT	–
6	4	0.3	–	NT	–
7	3	RAST 1	–	Epoxy paint: negative	–
8	7	< 0.3	–	NT	–
9	7	0	–	Epoxy glue: negative	–
10	4	0	ACD	NT	–
11	4	< 0.3	–	NT	–
12	3	< 0.3	–	NT	–
13	6	ND	–	NT	–
14	5	ND	–	NT	–
15	4	ND	–	NT	–
16	3	ND	–	NT	–
17	3	ND	–	NT	–
18	3	ND	–	NT	–
19	3	ND	–	NT	–

ACD, allergic contact dermatitis; HSA, human serum albumin; ND, not determined; NT, not tested; RAST, radio-allergosorbent test.

Concomitant prick test reactions/positive IgE levels can be explained by cross-sensitization or simultaneous exposure to several different isocyanates. The latter alternative is common in work environments. As expected, asthma was the most common diagnosis, but the present study population also includes 5 cases of rhinitis and 3 of contact urticaria. One of the urticaria cases (no. 11) has been previously reported (9). In addition, other centres have reported 2 contact urticaria cases associated with isocyanate-specific IgE (15, 16).

Epoxy resins

Positive prick test reactions and specific IgE for DGEBA epoxy resin have been described in some earlier FIOH reports (10, 17). In the present study population, 19 patients with positive prick test reactions to DGEBA–HSA conjugate were detected, but only two relevant occupational diseases were diagnosed among them. It is noteworthy that several patients had allergic contact dermatitis caused by epoxy resin, which might mask mild symptoms of contact urticaria. DGEBA-specific IgE was found in 6 (32%) of the patients. According to the FIOH experience, IgE-mediated sensitization to DGEBA seems to exist, although it is rare, and prick testing with DGEBA–HSA conjugates may be considered in patients with typical symptoms. However, one must bear in mind that many positive reactions do not have clear clinical relevance. Respiratory symptoms connected to epoxy

resin systems may also be explained by IgE-mediated allergy to acid anhydride curing agents.

Amine hardeners for epoxy resins

We were not able to find any reports on positive reactions to the amine hardeners prick tested in the series. Our study resulted in several small prick test reactions to some of the amine hardeners tested as coca/glycerin solutions, but they were not associated with an occupational disease. The amine hardeners are alkaline, which might elicit some irritant reactions, but the true significance of these small reactions remains unclear.

Chloramine-T

Chloramine-T is a disinfectant and a well-known cause of occupational asthma (18–20). There are also reports of occupational rhinitis (20) and contact urticaria (21). Specific IgE can usually be found in these cases, and prick testing is a commonly used method to diagnose sensitization to chloramine-T (18–21). The present study population includes 10 patients (nos. 1–10) with positive prick test reactions to chloramine-T–HSA conjugates and specific IgE. However, only 4 of these patients were diagnosed with an occupational disease. In addition, 6 patients (nos. 11–16) had positive reactions only to the 1% chloramine-T solution, and did not show specific IgE. These reactions were possibly irritant reactions.

Table 5. Patients with positive prick test reactions to persulfates: prick test reactions, persulfate-related diagnoses, and reactions in specific inhalation challenge tests and other provocation tests

Patient	Prick (mm)		Persulfate-related diagnosis	Specific inhalation challenge	Other provocation tests
	Ammonium persulfate	Potassium persulfate			
1	5	5	Rhinitis	Bleaching powder: rhinitis and urticarial reaction	NT
2	3	4	Contact urticaria	Bleaching powder: negative	Open skin application positive
3	12	8	Contact urticaria	Ammonium persulfate: asthmatic reaction	NT
4	6	6	Asthma	NT	Nasal challenge with ammonium persulfate positive
			Rhinitis		
5	3	0	Contact urticaria	Bleaching powder: rhinitis and urticarial reaction	Open skin application with ammonium persulfate positive
			Rhinitis		
			Asthma		
6	3	3	Contact urticaria	NT	Nasal challenge with ammonium persulfate negative
7	4	4	–	Bleaching powder: negative	NT
8	6	6	–	Bleaching powder: negative	NT
9	3	4	–	Bleaching powder: negative	NT
10	4	3	Contact urticaria	NT	Open skin application with ammonium persulfate positive
11	7	8	Rhinitis	Bleaching powder: negative (borderline rhinitis reaction)	Nasal challenge with ammonium persulfate positive
12	3	2	Contact urticaria	Bleaching powder: asthmatic reaction	NT
13	5	5	Asthma	NT	NT
14	7	NT	Contact urticaria	Ammonium persulfate: negative	NT
			Rhinitis		
15	5	5	Contact urticaria	Bleaching powder: negative	NT
16	5	4	–	Bleaching powder: rhinitis reaction	NT
			Rhinitis		
17	3	4	Contact urticaria	Bleaching powder: negative	NT
			–		

NT, not tested.

The present results show that the 1% solution can be used in prick testing, but that HSA conjugates might be more specific for sensitization. A patient of Wass et al. reacted in prick tests to chloramine-T–HSA conjugates at lower concentrations than chloramine-T/saline/glycerol solution (22). This case supports the better specificity of the HSA conjugates.

Persulfates

Prior studies have provided controversial information on the value of prick tests in the diagnosis of persulfate-related asthma, rhinitis, and contact urticaria. Moscato et al. (23) found no positive prick test reactions in 26 hairdressers with occupational asthma caused by persulfates, and nor did Diab et al. in a study in which 29 hairdressers underwent prick tests with persulfates (24). Other studies have reported positive prick test reactions in a substantial proportion of the patients tested (25, 26). The variation of the persulfate concentrations of the test solutions (0.05–5%) may have influenced the results in these studies. At the FIOH, prick tests with a persulfate concentration of 2% in water were positive in 17 patients; 11 (65%) of them were diagnosed with an occupational disease, most often contact urticaria and rhinitis. We did not determine persulfate-specific IgE. In 6 patients, prick tests indicated sensitization, but no occupational disease was diagnosed. It is difficult to assess the relevance of these positive test results and whether they reflected sensitization or represented unspecific irritant reactions. In the literature, specific IgE has been reported only occasionally (26). It is difficult to prepare HSA conjugates of persulfate salts, but persulfates diluted in HSA solution could be tried for prick testing.

Other hairdressing chemicals

PPD and its derivatives used in permanent hair dyes are well known for their ability to induce contact allergy, and cases of anaphylaxis have also been described. We found only a few reports on positive prick test reactions to PPD (27–29).

Ammonium thioglycolate and pyrocatechol elicited no positive prick test reactions, and nor were we able to find any reports on positive prick test reactions or specific IgE for these substances in the literature.

Chlorhexidine

There are many reports on chlorhexidine-induced anaphylaxis during surgical operations and other medical procedures (30). Immediate sensitization to chlorhexidine resulting from occupational exposure appears to be

rare, but should be kept in mind, especially in dentistry and healthcare workers (31, 32). Although small prick test reactions without clinical significance have been seen (33), the present literature supports the use of prick testing in the diagnosis of immediate hypersensitivity reactions to chlorhexidine together with assays for specific IgE (33–35). Commercial assays for the determination of chlorhexidine-specific IgE are currently available.

Aziridine

PFA compounds are used as hardeners in surface coatings. Positive prick test reactions to 1% PFA in water have been reported by the FIOH (12, 36) and in Italy (37), but, as far as we know, specific IgE has not been shown. However, it is difficult to draw definite conclusions, as exposure to PFA is rare and the number of tested patients is small. We continue to test exposed patients with the water solutions and the HSA conjugate.

Methacrylates

Methacrylates are well-known contact allergens, and have been associated with occupational asthma cases (38). However, we found no reports on positive prick test reactions or specific IgE in the literature. Moreover, the present analysis does not support the use of prick testing for diagnosing occupational diseases caused by methacrylates. Methacrylates probably induce occupational asthma through non-IgE-dependent mechanisms (39).

Ethanolamines

Ethanolamine-containing products include metal-working fluids and cleaning agents. The FIOH has reported 2 occupational asthma cases caused by ethanolamines (40, 41), but positive prick test reactions or ethanolamine-specific IgE have not been described. The present analysis did not change the situation. The mechanism of ethanolamine-related asthma might not involve IgE-mediated sensitization.

Formaldehyde

Induction of specific IgE associated with exposure to formaldehyde has been described as a rare finding in asthmatic children (42) and in connection with dental root canal sealants (43), and it is also rare following occupational exposure (44). The clinical significance of specific IgE remains unclear, as the production of IgE does not seem to correlate with symptoms related to formaldehyde exposure (45). Only a few case reports of

positive prick test reactions to formaldehyde are available, mainly in patients with severe allergic reactions to dental root canal sealants (43, 46, 47). We found no clearly positive prick test reactions to formaldehyde. All of the reactions were smaller than the control wheal, and there was no evidence of specific IgE in the patients tested. The results suggest that irritation is the main cause of the reactions, and distinguishing a possible allergic reaction is difficult. Hence, prick testing cannot be considered to be a reliable method for diagnosing IgE-mediated allergy to formaldehyde, at least not in occupational settings.

Other aldehydes

Glutaraldehyde is used for sterilization in healthcare settings, and has been associated with occupational asthma. Glutaraldehyde-specific IgE has been a sporadic finding in previous reports (48, 49). The correlation between glutaraldehyde-related symptoms and glutaraldehyde-specific IgE seems to be quite weak (50). We were not able to find earlier reports on positive prick test reactions to glutaraldehyde in the literature, and the two positive reactions in our study population were not associated with an occupational disease. Our conclusion is that the role of IgE-mediated allergy in glutaraldehyde-related symptoms remains unclear, and that prick testing cannot be considered to be a relevant diagnostic method for evaluating these symptoms.

Glyoxal is a disinfectant used in medical care and dentistry, and a contact sensitizer. We are not aware of any reports of positive prick test reactions, specific IgE, or asthma caused by glyoxal exposure.

Colophonium and related substances

Colophony (rosin) is a complex mixture of resin acids derived from pine trees. Contact allergy to colophonium is common, and abietic acid is the main contact allergen in colophony. Inhalation of colophonium fumes can induce occupational asthma (51, 52). A case of contact urticaria caused by colophonium with a positive prick test reaction to a 20% patch test substance (pet.) has been reported (53). Elms et al. detected specific IgE in colophonium-exposed workers with respiratory symptoms (54), but we did not find other reports on specific IgE. The clinical relevance of the few small positive reactions in our study population remained doubtful, so prick testing cannot be considered to be an important tool for diagnosing occupational diseases caused by colophonium.

General Remarks

We analysed a wide-ranging study population regarding prick tests performed with chemicals, in order to

evaluate the feasibility of prick testing for the diagnosis of occupational respiratory diseases and contact urticaria caused by chemicals. In the present study, we did not include carboxylic acid anhydrides, which regularly elicit positive prick test reactions in sensitized patients. Because of the retrospective nature of the study and the 20-year long study period, substantial variation in clinical methods, such as the methods used in determination of IgE, is inevitable, which limits the possibilities of generalizing the results. The prick test solutions used were prepared in our own laboratory, and are therefore not commercially standardized. Most of the chemicals have been tested in hundreds of patients, and the vast majority of the test results have been negative. These negative test results provide a considerable amount of control material. However, some of the chemicals elicited a substantial number of (usually small) reactions without clear clinical relevance, which affects the feasibility of the respective test.

Positive prick test reactions to isocyanate–HSA conjugates were combined with isocyanate-specific IgE, and a relevant occupational disease was also diagnosed in almost all of the prick test-positive patients. However, it is important to remember that prick tests and specific IgE are positive in only a minority of isocyanate asthma cases. Prick testing with chloramine-T also appeared to be useful: positive prick test reactions to chloramine-T–HSA conjugates were especially associated with chloramine-T-specific IgE, although a relevant occupational disease was not diagnosed in every positive patient. Simple chloramine-T water solutions can also be used, but they seem to elicit more non-specific possible irritant reactions. Patients with positive reactions to persulfate water solutions were often diagnosed with an occupational disease, but in ~30% of the patients no clear clinical relevance was found. Positive prick test reactions to DGEBA epoxy resin–HSA conjugates were associated with DGEBA-specific IgE in only a minority of the patients, and a relevant occupational disease was diagnosed even less frequently.

The prick test results with chloramine-T imply that chemical–HSA conjugates may be more specific indicators of IgE-mediated sensitization. It might be worth testing persulfate–HSA conjugates, for example. On the other hand, prick tests with DGEBA epoxy resin show that irrelevant reactions also occur with HSA conjugates.

Some chemicals caused small prick test reactions that met the criteria for a positive reaction, but that were smaller than the histamine reaction. This was most common for formaldehyde and the amine hardener group. Water-based solutions seemed, in general, to provoke

small non-specific reactions more often than HSA conjugates. Amine hardeners and chloramine-T are both alkaline substances, which might result in irritation when they are used in prick testing. The concentration of the chemical is also higher in the coca/glycerin solution than in the HSA-conjugate. The small reactions correlated poorly with specific IgE and with the clinical symptoms of the patients, and the clinical relevance of these minor reactions remains doubtful.

During the 20-year study period, no severe adverse reactions were seen at our clinic. In the literature, some anaphylactic reactions have been described following prick testing with chemicals, but in these cases the patient's symptoms prior to the prick test were particularly strong, which is usually not the case in occupational settings. Prick tests can be started at very low concentrations, to guarantee the safety of a patient with severe symptoms. It is, of course, important to reduce the number of tested substances in these patients, concentrate on the most probable candidates for causative agents, and proceed stepwise. Our experience implies that prick testing with chemicals is safe.

At the FIOH, we have used prick tests extensively and also tested patients with only a mild suspicion of an occupational disease caused by chemicals. Consequently, the group of all individuals prick tested does not directly correspond to the group of individuals with significant exposure to each group of chemicals. This may at least partly

explain the low percentages of positive reactions. Despite the wide use of chemical prick testing at the FIOH, these tests are generally not essential in the diagnosis of occupational respiratory diseases. Many chemicals induce occupational asthma through non-IgE-mediated mechanisms, and the diagnoses were mainly based on specific inhalation challenge, performed in accordance with the published and chemical-specific house guidelines (39, 55, 56). This test is considered to be the reference standard in the diagnosis of occupational asthma and rhinitis, and thus reliably confirms the occupational disease; however, false-negative results may occur.

The results of our study have been used to further develop the prick testing routines at our clinic. On the basis of these results, we have decided to give up prick testing performed with acrylates, amines, ethanolamines, colophonium, and tall resin. The usefulness of these tests is doubtful.

In conclusion, prick testing provides a fast and complementary tool for diagnosing work-related diseases caused by some chemicals, but the results should be carefully interpreted and related to clinical symptoms and other diagnostic tests.

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