

Occupational respiratory hypersensitivity caused by preparations containing acrylates in dental personnel

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Summary

Background Allergic contact dermatitis caused by acrylate compounds is common in dental personnel; they also often complain of work-related respiratory or conjunctival symptoms.

Objective The aim of the present study was to report the cases of acrylates induced respiratory hypersensitivity in dental personnel diagnosed in Finland during the last 6 years.

Methods Occupational asthma, rhinitis, laryngitis and pharyngitis cases were diagnosed according to patient history, PEF monitoring, and a work-simulating provocation test.

Results Twelve cases of respiratory hypersensitivity caused by acrylates diagnosed in dental personnel (six dentists and six dental nurses) in 1992–97 are reported. During this period one case of conjunctivitis and one of laryngitis have been published separately. Nine cases of occupational asthma, two rhinitis cases, and one laryngitis case were verified according to the challenge tests with dental acrylate compounds (acrylates, methacrylates and epoxy acrylates). Only three patients had positive skin-prick test reactions to common environmental allergens, and none reacted to acrylates in the skin-prick tests. Five patients had an elevated total IgE (>110 kU/L). PEF follow-up showed an occupational effect in all examined eight patients with diagnosed asthma. The mean duration of exposure to acrylates was 22 years, and the duration of respiratory symptoms 8 years.

Conclusions The results indicate that acrylates constitute an important hazard for dental workers. The mechanism of respiratory hypersensitivity is still unknown, and it is probably not IgE-mediated.

Keywords: occupational asthma, rhinitis, pharyngitis, laryngitis, acrylates, methacrylates

Clinical and Experimental Allergy, Vol. 28, pp. 1404–1411. Submitted 18 November 1997; revised 7 April 1998; accepted 13 May 1998.

Introduction

The development of the methacrylate and acrylate compounds started in the 1930s, and they soon found extensive application in the manufacture of plastic glass (Plexiglass, Perspex, Lucite) used in aircrafts, paints, coatings, and printing inks, as well as in dentistry [1–3]. Today acrylates have a wide application in various products, such as the manufacture of dental prostheses and tooth fillings, printing colours, lacquers, paints, orthopedic prostheses and splints, soft contact lenses, histological preparations, floor waxes,

floor coatings, surface treatments of leather, textiles and paper products, nail cosmetics, and as glues, sealants and adhesives [1–3]. As acrylates are well known contact allergens [1–3] and can also induce respiratory hypersensitivity [4,5], sensitization may develop from a wide variety of products in different occupations.

Acrylates are esters of acrylic acid, and methacrylates are esters of methacrylic acid. Three groups of acrylates are important in dentistry: (a) monofunctional methacrylates such as methyl methacrylate (MMA) and 2-hydroxyethyl methacrylate (2-HEMA) (b) multifunctional methacrylates such as ethyleneglycol dimethacrylate (EGDMA) and triethyleneglycol dimethacrylate (TREGDMA), and (c) acrylated and methacrylated prepolymers such as

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2,2-bis[4-(2-hydroxy-3-methacryloxypropoxy)phenyl]propane (BIS-GMA) and urethane dimethacrylate [1–3].

Skin sensitization from MMA in dental acrylates was reported already in the 1940s [6]. The newer acrylates are probably stronger sensitizers than MMA [1–4,7,8]. Dental personnel are at considerable risk of developing occupational allergy to acrylates. Dental acrylic products such as prostheses [7,8], dental composite resins [9] and dentin bonding agents [10,11] have caused occupational allergic contact dermatitis (ACD). Clinically, the dermatitis often appears as pulpitis of the fingertips, although wide-spread dermatitis is also seen. Dermatitis of the face and eyelids may be caused by airborne particles of acrylates [12]. In dental work also some cases of respiratory hypersensitivity, e.g. pharyngitis [4,13], laryngitis [14] and asthma [4,15,16] as well as conjunctivitis [8] have been reported. In the present paper we report 12 cases of respiratory hypersensitivity caused by acrylates in dental personnel.

Methods

Flow-volume spirometry was performed with a rolling seal spirometer (Mijnhardt, Vicatest 3) connected to a micro-computer (Medicro MR-3), and Viljanen's reference values were used [17]. Histamine challenge tests were performed according to Sovijärvi's method [18] following FEV₁ (Forced expiratory volume in one second) values with a Vitalograph S bellow spirometer (Vitalograph, Buckingham, UK). A 15% reduction in FEV₁ was considered significant and the provocative dose of histamine diphosphate causing a 15% reduction in FEV₁ (PD₁₅) was measured. The hyperresponsiveness was graded as strong with PD₁₅ < 0.10 mg, moderate with 0.11–0.40 mg and slight with 0.41–1.6 mg. The long-term peak expiratory flow (PEF) monitoring at the workplace and on days off was made according to the method of Burge [19] and the occupational effect was evaluated visually from the plotted presentation [20].

Skin-prick tests to common environmental allergens were performed using a previously described method [21]. All patients were also tested with natural rubber latex gloves [22], and a commercial latex extract (Stallergenes S.A., Fresnes Cedex, France); tests with chloramine T were done if there was a positive work history also [23]. Skin-prick tests with methyl methacrylate (MMA), 2-hydroxy-methyl methacrylate (2-HEMA), bisfenol-A-diglycidyl-ether-methacrylate (BIS-GMA), ethyleneglycol dimethacrylate (EGDMA) and triethyleneglycol dimethacrylate (TREGDMA) were done with human serum albumin (HSA) conjugates as previously described [24]. The skin-patch tests to acrylates were done with the occlusive Finn Chamber^R technique [25].

Inhalation challenge tests with a placebo and dental acrylate compounds (mixtures in liquid or powder form) were performed in a 6 m³ challenge chamber according to the international guidelines [26,27]. If the acrylate compound was in liquid form, the patient handled the compound for 30 min as follows: six drops of the dental primer and 6 drops of the dental adhesive were added simultaneously for 10 min; two drops of each were then added in turn for 5 min, and repeated once. If the challenge test was negative, the challenge test was repeated on another day with a double dose of both substances. The control challenge test was done with polyol (Hydrogenated decene oligomers, Nexbase 200 6FG, Neste PAO NV, Beringen, Belgium) if the agent tested was in fluid form, and with lactose if it was in powder form. The FEV₁ and PEF values during the challenge test procedure were measured by a portable pocket-size spirometer (Micro Plus Spirometer, Micro Medical, UK) [28]. In case of patients 1 and 2, the PEF values were followed up with a Wright peak flow meter (Clement Clarke M286, Ferraris Medical) and the FEV₁ values with a Vitalograph S bellow spirometer (Vitalograph, Buckingham, UK) according to a method reported earlier [29]. The clinical symptoms and lung auscultation were recorded, as well.

The mucosal response of the nose during the challenge tests was registered, and nasal blockage and rhinorrhoea were scored before and after the provocation test according to a method by Hytönen and Sala [30]. Physiological measurements were also used in the recording of the change in the nasal blockage either by rhinomanometry (Rhinomanometer NRG, Mercury Electronics, Glasgow, UK) or acoustic rhinometry (RHIN2000, SR Electronics APS, Lyngby, Denmark) [31]. The nasal response was considered positive if the status change and physiological measurement criteria were fulfilled [30,31]. A scoring method was used in the evaluation of the laryngeal and pharyngeal response [13,14]. The ocular reaction was followed and evaluated by an ophthalmologist as described earlier [8].

Results

We diagnosed 12 patients in dental professions (six dental nurses and six dentists) to have respiratory and mucosal hypersensitivity caused by acrylates: nine had asthma, two rhinitis, and one laryngitis, caused by acrylate compounds during 1992–97. Most patients were involved with dental care, dental fillings and orthodontics. One dentist (patient no. 6) was also engaged with dental prostheses. The age of the patients was 47.3 ± 9.5 years (mean $\pm$ SD), the duration of exposure to acrylates in the dental profession was 21.8 ± 7.4 years. The duration of acrylate exposure before the onset of the symptoms caused by acrylates was 13.5 ± 8.9 years, and the duration of symptoms was

8.3 $\pm$ 7.5 years (range 1–23 years). At the time of the diagnosis, spirometry was normal in nine of the patients, and three showed slight obstruction without significant response to bronchodilator. Histamine challenge test showed moderate bronchial hyperreactivity in one and slight bronchial hyperreactivity in three, but the remaining eight did not display any bronchial hyperreactivity. Only one of our 12 patients (patient no. 5) had allergic contact eczema caused by ethyl acrylate caused by prosthetic work diagnosed 12 years before the present examinations. The other patients had no contact eczema associated with the use of acrylates. One patient had conjunctivitis caused by methacrylates in addition to the acrylate-induced asthma (patient no. 5). Also, contact urticaria caused by natural rubber (NRL) latex was verified in patient no. 4. Otherwise the patients did not show positive skin-test reactions to NRL. The allergological data on the patients are presented in Tables 1 and 2. Two cases are described in detail, one as an example of late reaction in challenge test and one of diagnostic PEF monitoring.

Patient no. 8 was a previously healthy 48-year-old dental nurse who had worked since 1967 in dentistry. Her work involved the mixing of dental composite resin products and the preparation of dental gypsum forms. The exposure to various acrylates had lasted for about 27 years. In 1993 she started to experience hoarseness and soreness of the throat, nasal stuffiness and dyspnoea, especially when preparing orthodontal fixatives. In 1994, spirometry was normal, histamine challenge test showed slight bronchial hyperreactivity, and PD₁₅ was 0.48 mg. In a clinical exercise test no indications of coronary heart disease nor asthmatic reaction were found. Skin-prick tests to common allergens, acrylates, chloramine-T and latex were negative. Inhalation challenge test with Scotchbond^R primer and adhesive, containing 2-HEMA and BIS-GMA (3M Company, St Paul, MN, USA) did not reduce lung function test results, nor nasal or pharyngeal status. Inhalation challenge test with Paladur^R (methyl methacrylate) (Heraeus Kulzer, Wehrheim, Germany) liquid and powder (polymethyl methacrylate) induced mucosal changes and symptoms of the upper respiratory tract, diagnosed as immediate hypersensitivity rhinitis and pharyngitis. The airflow resistance in rhinomanometry increased significantly (70%) after the challenge test. The challenge test did not induce significant reactions in FEV₁, but 16 h after the challenge test PEF was reduced by 20%. Based on these findings, occupational hypersensitivity rhinitis and pharyngitis caused by dental acrylate compounds were diagnosed. At this time the PEF monitoring did not show variation between workdays and leave days.

The patient continued working in conditions of lowered exposure to acrylates, using nasal fluticasone dipropionate and inhaled budesonide dipropionate 800 μ g a day. In spring 1995, PEF monitoring showed a variation

of 350–470 L/min during work days and 420–460 L/min on days off, regarded as diagnostic for occupational asthma caused by acrylate compounds (Fig. 1). The histamine challenge test showed no bronchial hyperreactivity after 1 year of treatment with an inhaled steroid. Inhaled budesonide and salbutamol were continued, and total avoidance of exposure to acrylate compounds was considered necessary because of her occupational rhinitis, pharyngitis and asthma.

Patient no. 12 was a 49-year-old woman who had worked as a dental nurse since the early 1970s. Earlier, idiopathic left vocal paralysis had been found, otherwise she was healthy. In the beginning of 1996, she felt slight rhinitis symptoms, and in April 1996 the symptoms of dyspnoea appeared when she was handling acrylate compounds. In June 1996, treatment of inhaled fluticasone dipropionate and salmeterol had been started.

In spirometry, slight partially variable central obstruction was found, caused by the vocal cord paralysis. No bronchial hyperreactivity was found in histamine challenge test. PEF monitoring showed increased (>20%) variation during working days. In the bronchial challenge test with Scotchbond^R primer and adhesive (3M Company) (10 drops of both) no significant reduction in PEF or FEV₁ (maximally –11%/–9%) was found. The challenge test was repeated with 20 drops of both substances; a maximal reduction of FEV₁ by 24% was measured 6 h after the challenge test (Fig. 2). On the day after the challenge test, the lung functions had returned to prechallenge level, indicating specificity of the challenge test reaction. In the control challenge test no reduction of PEF or FEV₁ was found. Inhaled fluticasone dipropionate, 500 μ g a day, was not discontinued during the challenge test. On the basis of the history, PEF monitoring, and the specific challenge test, a diagnosis of occupational asthma caused by dental acrylate compounds was made. Inhaled fluticasone, salmeterol and salbutamol medications were continued, and avoidance of acrylate exposure was recommended.

Discussion

According to the Finnish Register of Occupational Diseases, the annual incidence of occupational asthma in 1990–95 was 18/100 000. The incidence of occupational asthma in dental workers was at the same time slightly higher, 23/100 000. In addition to acrylate compounds, which were the causative agents in seven patients, other major causes in dental workers were natural rubber latex and disinfectants, e.g. chloramine-T. A recent study shows the increasing incidence of occupational asthma in the dental profession in Finland [32]: in 1982–84 one case of occupational asthma was reported to the Finnish Register of Occupational Diseases, in 1986–88 no cases and in 1992–4, 19 cases were

Table 1. Characteristics of patients (1–5) suffering from respiratory diseases caused by acrylate compounds. p, primer; a, adhesive; Mm1, Methacrylate mixture: primer containing HEMA (2-hydroxy ethyl methacrylate) 40% and adhesive containing 62% BisGMA (Bisfenole-A-diglycidyl-ether methacrylate) and HEMA 37%; Mm2, Methacrylate mixture 2: TREDGMA (triethyleneglycol dimethacrylate) 40–50%, BIS-GMA 50–60%. *Clinical diagnosis, **major diagnostic criteria for asthma; d, drops. Prick positivity means one or more positive reactions in standard series.

Patient	1	2	3	4	5	6
Age	41	48	61	30	51	51
Gender	Male	Male	Female	Female	Female	Female
Profession	Dentist	Dentist	Dentist	Dental nurse	Dentist	Dentist
Smoker	No	No	No	Yes	No	No
Atopy history own/family	Yes/yes	No/Yes	No/Yes	Yes/No	No/Yes	No/Yes
Duration of exposure to acrylics (years)	20	22	24	5	30	27
Duration of symptoms (years)	4	3	22	2	13	23
Prick positivity	Yes	No	No	Yes	No	No
IgE (kU/L)	296	83	289	105	14	17
Spirometry	Normal	Normal	Normal	Normal	Normal	Normal
Histamine challenge test (PD ₁₅)	>1.6 mg	>1.6 mg	>1.6 mg	>1.6 mg	>1.6 mg	>1.6 mg
Causative product	Scotchbond 7502A	Rely-A-Bond paste	Scotchbond multipurpose p + a	Scotchbond dc 7533R; Scotchbond 7502A	Delton	Paladur Forestacryl
Ingredients	Mm2	BIS-GMA HEMA	Mm1	Mm2	TREDGMA EDGMA, DEGDA BIS-GMA	Methyl methacrylate
Challenge dose	10 d + 10 d	1 d + 12 d	20 d + 20 d	10 d + 10 d	TREDGMA 3d BisGMA 7d	Prosthesis dose of powder
Mode of FEV ₁ /PEF reaction	Late	Immediate	Late		Late	
Max FEV ₁ /PEF reduction	14%/13%	–/16%	20%/20%**		11%/28%	
Occupational effect in PEF	Not studied	Yes**	Yes	Not studied	Yes**	No
Diagnosis	Asthma Rhinitis*	Asthma Pharyngitis* Laryngitis*	Asthma	Rhinitis* Contact urticaria (latex)	Asthma Conjunctivitis*	Laryngitis*
Year of diagnosis	1992	1993	1994	1994	1994	1995

Table 2. Characteristics of patients 6–11. p, primer; a, adhesive; HEMA, 2-hydroxy ethyl methacrylate, BIS-GMA, Bisfenole-A-diglycidyl-ether-methacrylate, TREDGMA, triethyleneglycol dimethacrylate, EDGMA, Ethylene glycon methacrylate, DEGDA, Diethylene glycol diacrylate, Mm1, Methacrylate mixture: primer containing HEMA 40% and adhesive containing 62% BisGMA and HEMA 37%, *Clinical diagnosis; **major diagnostic criteria for asthma, d, drops. Prick positivity means one or more positive reactions in standard series.

Patient	7	8	9	10	11	12
Age	53	48	61	41	34	49
Gender	Female	Female	Female	Female	Female	Female
Profession	Dental nurse	Dental nurse	Dentist	Dental nurse	Dental nurse	Dental nurse
Smoker	No	No	No	No	No	No
Atopy-history own/family	No/No	No/No	No/No	No/No	Yes/Yes	No/Yes
Duration of exposure to acrylics (years)	22	27	25	22	10	28
Duration of symptoms (years)	5	2	10	6	9	1
Prick positivity	No	No	No	No	Yes	No
IgE (kU/l)	59	203	93	270	260	43
Spirometry	Normal	Normal	Slight obstruction	Slight obstruction	Normal	Slight obstruction
Histamine challenge (PD ₁₅)	>1.6 mg	0.48 mg	0.15 mg	0.72 mg	0.79	>1.6 mg
Causative product	Scotchbond multipurpose a	Paladur	Scotchbond multipurpose p + a	Scotchbond multipurpose p + a	Scotchbond multipurpose p + a	Scotchbond multipurpose p + a
Ingredients	BisGMA HEMA	Methyl methacrylate Powder 10 ml, liquid 10 d	Mm1	Mm1	Mm1	Mm1
Challenge dose	4 d	10 d + 10 d	20 d + 20 d	20 d + 20 d	20 d + 20 d	20 d + 20 d
Mode of FEV ₁ /PEF reaction	Immediate	Late	Late	Late	Late	Late
Max FEV ₁ /PEF reduction	5/18%	6%/20%	20%/16%		13%/17%	24%/13%**
Occupational effect in PEF	Yes**	Yes**	**Yes	No	Yes**	Yes
Diagnosis	Asthma	Asthma Rhinitis* Pharyngitis*	Asthma	Rhinitis*	Asthma	Asthma
Year of diagnosis	1995	1995	1995	1995	1996	1997

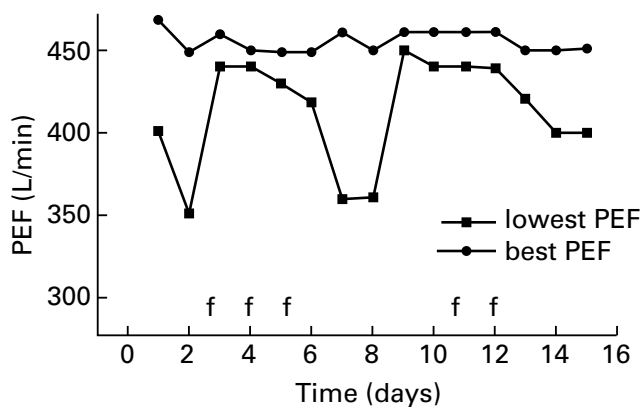


Fig. 1. PEF surveillance of patient no. 8. The lowest value of the day is presented with a square and the best values with a circle. F indicates the days off.

reported. This increase of occupational asthma is mostly due to acrylates. In 1985–91 we found three cases of respiratory hypersensitivity caused by acrylates in dental personnel [4,13], whereas in 1992–97 altogether 14 cases have been diagnosed. Two cases of acrylates caused respiratory or mucosal hypersensitivity have been published separately [8,14]. Twelve further cases of respiratory hypersensitivity induced by acrylates in dental personnel in Finland in 1992–97 are reported in the present paper. Reports of occupational hypersensitivity in dental personnel from other countries are scarce [15,16], although one would expect the problem to be similar in other industrialized countries.

In our patients, the duration of exposure was over 20 years, and the patients developed respiratory symptoms after about 14 years of exposure. The likely reason for the long latency period is the relatively sparse use of acrylates in the 1970s; their use did not become widespread until the 1980s. In any way, the latency period in occupational asthma caused by acrylates seems to be much longer than in asthma caused by other low molecular weight chemicals, such as di-isocyanates [33]. In the past decade new acrylate compounds have been taken into use [1–4,7,8]. These may be more potent sensitizers, which may be another reason for the increase in acrylate hypersensitivity.

In three patients, occupational asthma was diagnosed based on the inhalation provocation tests (FEV_1 reduction $\geq 20\%$) [27] combined with the patients' history of exposure and symptoms. Allergic rhinitis, laryngitis, pharyngitis or conjunctivitis were also diagnosed following tests in a provocation chamber. Eight out of nine patients diagnosed to have asthma showed a work-related effect of PEF recordings. In one patient with asthma, PEF monitoring was not performed. Thus, PEF monitoring seems to be valuable in the diagnostics of occupational asthma caused by acrylate compounds.

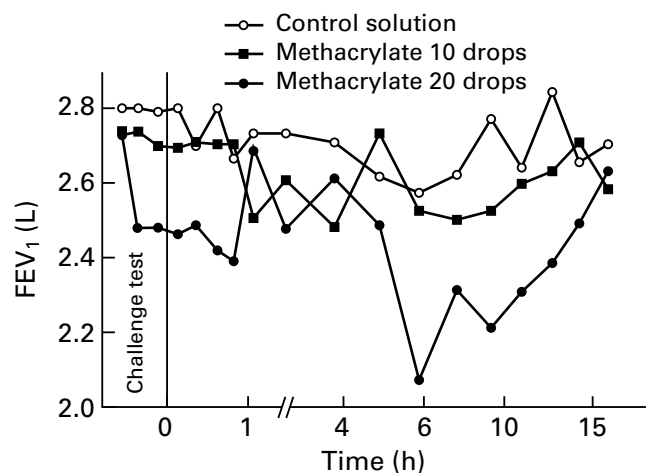


Fig. 2. The FEV_1 follow-up during the inhalation challenge tests of patient no. 12.

Patients 1 and 2 do not fulfil all the criteria of asthma (Table 1). They were examined according to the old follow-up method during the challenge procedure [29] when FEV_1 was not measured as often as PEF. The PEF monitoring of patient 1 could not be done because he was on sick leave. Asthma was diagnosed, based on the patient history and the suggestive challenge test reaction, and also because previous moderate bronchial hyperreactivity had disappeared before the present studies, which were conducted after about 1 year's sick leave and daily inhaled beclomethasone dipropionate (1000 μ g) medication. In the case of patient 2, simultaneous FEV_1 measurement during the maximal PEF reduction is missing. In his case, the findings supporting the diagnosis of asthma were the suggestively positive challenge test reaction, the patient history, and the PEF work place monitoring with about 20% variation during working days and $<10\%$ during days off.

In the present study, only three of the patients with occupational asthma reacted positively to histamine challenge test. According to Burge [34], 20% of patients with occupational asthma do not show bronchial hyperreactivity during non-specific challenge testing. Six out of nine patients with asthma had received inhaled steroids before the inhalation provocation tests, which decreases bronchial hyperreactivity. In addition, most of the asthmatics had been on sick leave before the provocation tests, which also might have influenced on the result in the histamine challenge test.

There is one report of acrylic acid to have caused positive immediate skin prick reaction with urticaria [35]. We have not so far found any positive immediate skin test reactions of acrylic compounds to compare with; all the present cases were skin-prick test negative. However, negative skin-prick test reactions do not exclude IgE-mediation. Negative

results may also depend on the skin-prick test material. HSA-conjugated skin-prick test substances [36] are produced mainly on a trial-and-error basis [37] and we cannot be certain that our conjugates are optimal to detect type I allergy. Acrylates are also known to be irritant. Acrylates are volatile liquids at room temperature and may irritate the respiratory tract. Rats exposed to 75 ppm of acrylic acid displayed damage to the nasal mucosa within 14 days, and mice showed similar damage at a much smaller, 5 ppm, dosage [38]. Therefore, the hypersensitivity reactions could be thought to be 'irritant'. However, we have challenged 36 other patients to dental acrylates without significant reaction in challenge test. Ten of them showed bronchial hyper-reactivity in histamine challenge testing. Thus, it is not likely that the challenge test reactions of the patients presented here would be irritant. In most of the patients the reduction in lung function occurred 6 or more hours after the challenge test. Only two patients had a maximal reduction in lung function immediately after the provocation, though the reduction in lung function was not significant in these. Our results do not explain the mechanism of acrylates induced asthma, although the late nature of the challenge test reactions may point to mechanisms other than IgE mediation.

The challenge tests were done with the dental acrylate resin products which contain other components as well as impurities. We have recently analysed products containing acrylates, and compared the results with the data given in material safety data sheets (MSDSs) or product declarations [39,40]. From an allergological point of view, the information given in MSDSs is insufficient. Recent studies [39,40] have reported that, e.g. 37% undeclared triethylene glycol dimethacrylate (TREGDMA) in a dental composite resin, 4.6% undeclared ethylene glycol dimethacrylate in a liquid used to make dental prostheses, 8.1% undeclared hydroxypropyl methacrylate in a reinforced composite resin and 26% undeclared 2-hydroxyethyl methacrylate in a glue. All the above acrylates are well-known sensitizers. Other undeclared allergens, e.g. epoxy resin, were present as well [39,40]. In the case of patient 6 the causative product also contained small amounts of dibutyl phthalate. Accordingly, dental personnel are exposed to many undeclared acrylates and other allergens. To ascertain what component is causing the asthmatic reactions, provocations with all the mentioned undeclared compounds ought to be undertaken. However, in this series of clinical challenge tests this was not practicable.

The present paper demonstrates the increasing problem of dental personnel developing respiratory hypersensitivity diseases during exposure to acrylate compounds. The long exposure time before the appearance of symptoms may be one reason why the number of published cases is low. The use of acrylates is steadily increasing, many new cases are anticipated. We diagnosed the first case of acrylate-induced

hypersensitivity in dental personnel in 1991 [4]. Since then the number of cases has increased conspicuously. The present paper demonstrates the importance of protecting dental personnel against acrylates and emphasizes the necessity of thorough examinations of their work-related respiratory symptoms. A new study has been undertaken by the authors to study the working conditions of dental personnel, their exposure levels to acrylates, and how to protect the airways from acrylates.

Acknowledgements

Thank you to Antti Karjalainen for calculating the incidence values from the Finnish Register of Occupational Diseases, and Timo Tuomi, for collecting the challenge test data for the 36 other patients challenged to dental acrylates.

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