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Four years of clinical experience with an adverse reaction unit for dental biomaterials

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Abstract – *Objectives:* We describe the function of, and results from, the Norwegian National Dental Biomaterials Adverse Reaction Unit after 4 years of activity from 1993 to 1997. *Methods:* During this period of time, 296 patients were examined at the unit, which is located at the Dental School, University of Bergen. The most prevalent age group was 40–49 years, and 70% were women. Dental amalgam was the primary reason for referral to the unit for nearly 85% of the patients, followed by metals in crowns and bridges (11%). Materials in removable dentures, resin-based filling materials and cements, endodontic materials, and others, including temporary materials, were also involved. Nearly all (96%) patients reported general subjective symptoms, such as muscle and joint pain, fatigue, and memory problems. Complaints involving the orofacial region (lips, face, temporomandibular joint) and intraoral subjective symptoms were also common. *Results:* Of the patients who were patch tested with substances in dental materials, 23% were positive to gold, 28% to nickel, 14% to cobalt, 9% to palladium, 6% to mercury, and 8% to one or more components of resin-based materials. Mercury concentrations in blood and urine were statistically higher in the patients with amalgam fillings compared with those without. *Conclusions:* Generally, we could not establish a straightforward cause-and-effect relationship between the presence of dental biomaterials and general symptoms. Twenty patients were advised to replace restorative materials because of contact lesions. Another 20 patients were recommended replacement of materials because of allergy verified with positive patch tests. The complex nature of most of the reactions requires a multidisciplinary approach to the care taking of patients who are concerned about reactions from dental materials, particularly amalgam.

Key words: adverse effects; allergy; dental amalgam; dental materials

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Dental materials are among the most extensively employed artificial materials for incorporation in the human body. They are classified as medical devices according to the European Medical Devices Directive (1). Dental treatment usually involves several materials that grow in number and complexity. Moreover, there is a shift away from amalgam as a restorative material in dental practice (2).

The frequency of adverse biologic reactions to dental materials in general practice is unknown, but is considered low, 1 : 700 to 1 : 2600 (3, 4). It is likely that the frequency is higher in specialist practices (5, 6).

A notable number of persons appear to be concerned about potential adverse effects of dental materials (7, 8). Partly as a response to the public concern about the safety of dental amalgam, the 'Dental Biomaterials Adverse Reaction Unit' was initiated by Norwegian health authorities in 1992 – the unit is a national resource unit in Norway, a country with about 3500 dentists serving a population of 4.5 million. The main task of the unit is to examine and evaluate patients with a wide range of complaints and disorders associated with dental biomaterials. The unit also encompasses a national adverse reaction registry, information activities aimed at the public and health professionals, as well

as research activities. Dental treatment is supposed to be performed by the patients' own dentist. The unit is funded by the Norwegian Ministry of Health, and the activity was organized by the University of Bergen. In 1999, the unit became a free-standing section with a full-time head of the activities. This unit was the first of its kind in dentistry. However, a regional 'Amalgam Unit' was in function at Huddinge Hospital, Sweden during 1993–1995 (9).

The aim of this paper is to describe the patients referred for clinical evaluation at the 'Dental Biomaterials Adverse Reaction Unit' in the time period from 1993 to 1997.

Materials and methods

The clinical team of the 'Dental Biomaterials Adverse Reaction Unit' consisted of one physician, one specialist in oral surgery and oral medicine, one dentist and one dental nurse, all part-time employed. The patients were seen during 1 day/week. During 1993–1999, the head of the unit was the professor of dental biomaterials (part-time employed, 40%), assisted by an administrative secretary.

Being a national unit, the patients' travel and accommodation expenses were covered. The existence of the unit was announced in the journals of the Norwegian Dental Association and the Norwegian Medical Association as well as through information material from the Norwegian Board of Health.

Referring procedures

A formal referral from a dentist or a physician was required. Following the referral, additional information (including laboratory tests) were obtained from the patients' own dentist and physician (Fig. 1). Thus, the collection of data is based on a decentralized procedure. All patients signed an informed consent agreement.

Patients

From September 1993 until the end of 1997, 296 patients with suspected adverse effects from dental materials were seen at the unit (Table 1).

Clinical evaluation

The patients answered a questionnaire concerning the case history and previous health problems. All patients underwent an oral and orofacial examination to reveal underlying oral diseases as a cause of their symptoms. A complete dental X-ray status was taken. The results of the oral examination is described elsewhere (10).

The patients had underwent a general medical examination by their own physician prior to the consultation at the unit. Routine blood analyses (white blood cell counts, hemoglobin, erythrocyte

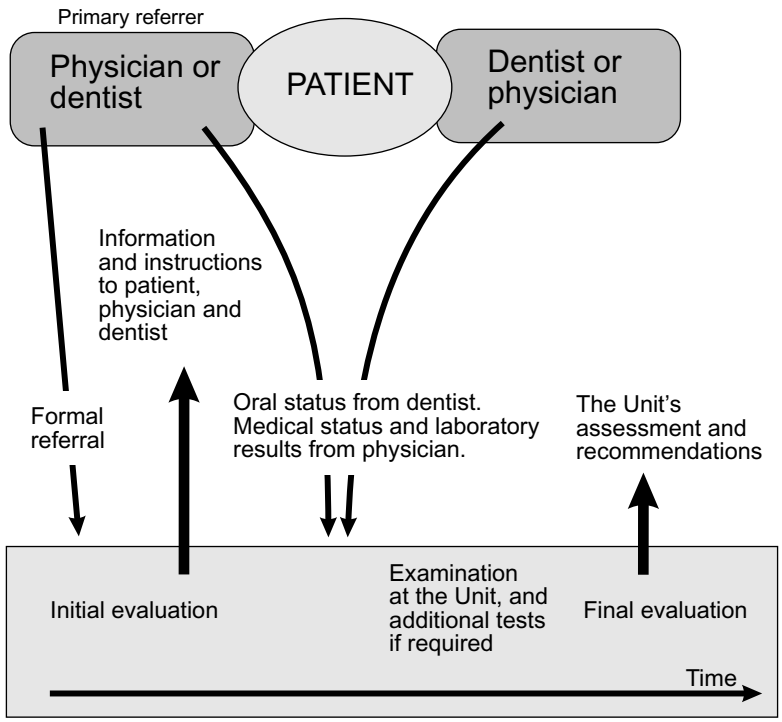

Fig. 1. Flowchart of routines of referral and clinical procedures used by the Dental Biomaterials Adverse Reaction Unit. Dentists or physicians can refer patients. After initial evaluation of the information in the referral, more specific information is requested from the patient's own dentist and physician.

Table 1. Number of patients referred to the Dental Biomaterials Adverse Reaction Unit during 1993–1997

	Females	Males	Total
Number of patients	208	88	296
Age (years: medians (lower–upper quartiles))	47 (39–53)	44 (35–55)	46 (38–54)
Dental materials associated with referral (% of patients)			
Amalgam	81.7	89.8	84.1
Metals and alloys in fixed restorations	12.9	6.8	11.1
Resin-based materials and cements	4.8	2.3	4.1
Materials in removable dentures	2.4	3.4	2.7

The most frequent reason for referral is given in percentage of patients. More than one reason could be given for each patient.

volume fraction, blood sedimentation rate, serum sodium, serum potassium, serum calcium, serum phosphate, serum creatinine, serum aminotransferases, serum iron, free T4 (thyroxin) fraction, thyroid stimulating hormone, and serum cobalamine were performed. Urine was investigated for presence of proteins, glucose, hemoglobin, white blood cells, and nitrates. Both spot urine samples (morning) and blood were analyzed for creatinine and mercury. The results of the different tests were compared with the reference values given by the medical laboratory, which performed most of the tests (11).

Patients with a history of allergy in general, eczema or suspected allergic reactions to dental biomaterials, were referred to a dermatologist. About 90% of these patients were assessed at the Department of Dermatology at Haukeland University Hospital in Bergen. Patch tests were performed with a dental series of test substances (DS-1000) in polyethylene chambers (IQ Chambers, Chemotechnique Diagnostics, Malmö, Sweden). The chambers were removed after 2 days, and test sites were read after 3 and 6 days, according to the International Contact Dermatitis Research Group (ICDRG) criteria (12).

Assessment and report to referring dentist and physician

Our aim was to supply knowledge-based information about the relation between dental materials and the suspected adverse effects and to suggest therapy for any medical or dental disorders.

The patients were informed about preliminary results upon leaving the unit. In weekly meetings, the clinical information for each patient was summarized and evaluated with regard to clinical significance. A report was sent to the patients' physician and dentist along with information to the patients. The patients were supposed to be informed by their dentist or physician about the clinical consequences regarding future treatment (Fig. 1).

Data description and statistical methods

Data were presented as medians and quartiles. The Wilcoxon–Mann–Whitney *U*-test was used for two-sample comparisons. Correlations were expressed by Spearman's Rank Correlation Coefficient (R_s). A *P*-value less than or equal to 0.05 was considered statistically significant. The statistical software SPSS (SPSS 6 Inc., Chicago, USA) was used.

Results

The 296 patients consisted of 70% women and 30% men. The age group of 40–49 years was the most prevalent. Dentists were the most frequent primary referrers with 223 patients, while 73 patients were referred by a physician.

Fifty-four per cent of the patients were part-time or full-time employed, 21% received disablement benefits on permanent basis, 4% were retired, 2% were unemployed, and 19% had partial or full-time sick leave. The patients had usually been in contact with the healthcare system for a long time without positive outcome regarding their condition. Thirty-five per cent of the patients had used complementary (alternative) health services.

Suspected amalgam-related health problems were by far (>80%) the most frequent reason for referral, followed by reactions associated with metals and alloys for fixed restorations (Table 1).

A majority of the patients ($n = 255$, 87%) had amalgam fillings, while 41 patients did not have amalgam fillings at the time of examination. Of those without amalgam, 34 patients (11.5%) had actively replaced their amalgam fillings because of symptoms assumed to be caused by amalgam, but without a positive outcome. Gold restorations ranging from small inlays to extensive bridges were present in 163 patients (55.4%). Nearly all patients (94%) had resin-based or cement fillings in one or more teeth.

The patients had a high prevalence of subjective symptoms associated with all regions of the body.

Table 2. Subjective general symptoms reported by the patients

Type of general subjective symptom	Occurrence of symptoms (% of patients)
Pain from muscles and/or joints	70
Fatigue	68
Dizziness and/or headache	66
Memory and concentration problems	52
Gastrointestinal symptoms	51
Anxiety. Depression	45
Visual disturbances	32
Cardiovascular symptoms	24
Hearing disturbances: tinnitus	22
Others	9
None	4

One patient could report several symptoms (296 patients).

Table 4. Subjective intraoral and orofacial symptoms reported by the patients

Type of subjective symptoms	Intraoral (% of patients)	Orofacial, lips and face (% of patients)
Pain and/or tenderness	40	36
Burning sensation	34	17
Feeling of stiffness and/or paresthesia	12	20
Taste disturbances	33	–
Dry mouth	41	–
Others	18	24
None	17	30

One patient could report several symptoms (296 patients).

General subjective complaints were reported by more than 90% of the patients (Table 2). Most patients did not present general objective findings, but 32 patients reported dermatitis and other skin problems.

Fifty per cent of the patients showed objective oral or orofacial findings, such as dysfunction of temporomandibular joints and various types of skin or mucosal reactions. Oral or orofacial subjective symptoms such as pain, tenderness, burning sensation, feeling of stiffness or paresthesia, taste disturbances and dry mouth were reported (Tables 3 and 4).

Among the selected patients ($n = 185$) who were referred to the dermatologist, positive test results to gold and nickel were seen most commonly (Table 5).

Results from routine laboratory tests of blood mostly fell within the reference ranges given, without specific patterns of deviations. Possible hypothyreosis was indicated in two patients. The median concentration of mercury was 6.0 μg/l in whole blood, and 2.0 μg/l in urine (3.3 μg/g creatinine; Table 6). Eleven patients had slightly elevated mercury levels in blood (14–22 μg/l), but with urinary mercury values within the reference range (11). Six patients had elevated mercury levels in urine (≥14 μg/l). One patient had a urinary mercury level of 48.2 μg/l. When related to creatinine, the result for this patient was 8.7 μg/g creatinine. Patients with amalgam fillings had statistically significant higher values of mercury in both urine ($P = 0.01$) and blood ($P = 0.04$; Table 6). Apart from a high number of amalgam fillings, these patients did not show subjective symptoms, objective findings or laboratory values differing from the rest of the patient population.

There was no significant correlation between mercury concentrations (blood and urine) and number of subjective symptoms or objective findings. Urinary mercury concentrations, adjusted for creatinine, showed a significant correlation to the number of amalgam surfaces ($R_s = 0.295$, $P < 0.01$), whereas there was no statistical correlation between mercury

Table 3. Objective orofacial and intraoral findings

Type of objective findings	Intraoral (% of patients)	Extraoral, lips, and face (% of patients)
Edemas	2	3
Wounds/vesicles	9	1
Rubor/erythema	12	4
Exanthem	–	8
Lichenoids	9	–
Atrophy	1	–
Others (temporomandibular joint dysfunction[a], gingivitis[b] amalgam tatoo, fordyce spots, linea alba)	24	38
None	50	50

One patient could report several signs (296 patients).
[a]Most common extraoral objective finding.
[b]Most common intraoral objective finding.

Table 5. Results of skin patch-testing

Patch test substance	Positive patch test results		
	Number of patients tested	Number of positive tested	% of positive tested
Nickel sulfate	185	52	28.1
Gold sodiumthiosulfate	172	39	22.7
Cobalt chloride	182	25	13.7
Palladium chloride	171	16	9.4
Mercury	181	11	6.0
Potassium dicromate	177	7	4.0
Colophony	178	5	2.8
Formaldehyde	177	4	2.3
Copper sulfate	179	3	1.7
Eugenol	177	2	1.1
Tin	170	1	0.6
Aluminum chloride hexahydrate	166	0	0.0
Components of resin-based materials (18 substances)	179	14	7.8

Patients could be positive to more than one test substance. Test substances from the dental screening test DS 1000 (Chemotechnique Diagnostics, Malmö, Sweden) are used.

Table 6. Mercury concentrations in urine, relative to creatinine, and in whole blood

	Mercury in urine: μg/g creatinine median/mean (25–75 percentile/max)	Mercury in blood: μg/l median/mean (25–75 percentile/max)
With amalgam	3.3/3.8 (1.8–5.1/20.7; $n = 230$)	6.0/6.2 (4.0–8.0/22.1; $n = 239$)
Without amalgam	2.4/2.5 (1.1–3.6/8.9; $n = 34$)	4.0/5.3 (2.0–8.0/16.1; $n = 36$)
Total population	3.1/3.6 (1.6–4.8/20.7; $n = 264$)	6.0/6.1 (4.0–8.0/22.1; $n = 275$)

Medians, arithmetic means, 25 and 75 percentiles, and maximal values are given. n = number of test results. Data for patients with and without dental amalgam fillings.

concentrations in blood and amalgam surfaces ($R_s = 0.084$, $P = 0.16$).

The group of patients who had actively replaced amalgam fillings ($n = 34$) had statistically higher number of subjective general symptoms ($P = 0.002$) as well as subjective orofacial symptoms ($P = 0.023$). Subjective intraoral symptoms were also higher, but not statistically significant ($P = 0.076$). Objective findings did not differ between the two groups ($P = 0.32$–0.90).

Patients with and without gold restorations were not statistically different regarding subjective symptoms or objective findings, except that the number of intraoral objective findings were higher in those with gold restorations ($P = 0.018$).

In 20 patients with contact lesions adjacent to dental materials, it was recommended to replace the materials. In another 20 patients with clinically relevant positive patch tests to constituents of dental restorations, it was suggested to consider replacement of those materials. Thirty-four patients with positive patch tests to constituents of restorative materials not currently used were recommended to avoid such materials in future dental treatment (Table 7).

Table 7. Recommendations given as a result of the evaluation at the unit

Type of recommendation	% of patients
Material related	
Replace materials in case of intraoral contact lesions adjacent to restorative materials	8
Replace materials because of a clinically relevant positive patch test	7
Avoid substances in future dental treatment due to positive patch test	12
Not material related	
Related to medical conditions	12
Related to oral conditions	7
Other	9
The assessment did not indicate specific health problems associated with dental materials	53

Several types of recommendations could be issued for one patient (296 patients).

In the unit's report to the dentists and physicians, recommendations were also given in relation to oral diseases, e.g. caries and periodontal conditions. Also, recommendations regarding medical conditions were given in some instances, e.g. hypothyreosis medication, need for evaluation of heart disease, medication of peptic ulcer (Table 7).

Discussion

The public's worry about side-effects caused by dental restorative materials has been mainly associated with dental amalgam (8). Poll measurements in Norway in 1995 (7) revealed that about 50% of the respondents associated amalgam with medium to severe health risks, while less than 10% regarded resin-based materials as a source of side-effects. The fact that 85% of our patients were referred because of symptoms allegedly caused by dental amalgam reflected this opinion.

The group of referred patients was heterogeneous, with complaints ranging from specific dental problems to unspecific general symptoms. Most patients presented a multitude of symptoms. A few patients with known chronic diseases, such as multiple sclerosis or other neurologic conditions, were concerned about the potential relationship between dental amalgams and the disease. More than 90% of the patients had general subjective symptoms; however, no causal relationship between general symptoms and dental materials could be established. The type of symptoms and lack of conclusive relationships are in accordance with several other studies (13–15).

The fact that 40% of the patients received disablement benefits or were on sick leave reflects a definite impairment in quality of life. Other studies on patients with self-reported 'amalgam illness' have suggested that the patients show clinical patterns similar to those of somatizing patients (16, 17). Patients with complaints related to dental amalgam have been shown to exhibit higher levels of psychic distress, a higher incidence of depression and somatization disorders as well as different styles of coping with anxiety (18). We did not perform routine psychologic or psychiatric evaluation. However, there is no doubt about the patients' suffering, but causal relationships to dental biomaterials could in general not be established, based on our approach.

Routine laboratory tests of blood and urine did not in general reveal specific pathologic conditions in the patients. After the introduction of obligate consultation at the patients' own dentist and physician, obvious dental and medical disorders were most likely treated prior to referral. It is crucial to perform a general medical examination in order to exclude, as far as possible, underlying nondental causes of the patients' ill-health.

Five patients had elevated values of mercury in urine. When related to creatinine content (19), the highest urinary mercury concentration reached values seen in chloralkali workers (20). However, the mercury concentrations were below levels associated with neurologic effects (21, 22). The patients with elevated mercury levels in blood had normal values of urinary mercury, indicating organic mercury originated from food, e.g. fish (23–25).

Oral and orofacial subjective symptoms also cover a wide range in these patients. Oral symptoms and findings are discussed in a separate paper (10). Generally, the patients suffered from pain and sensational disturbances, including dry mouth and 'burning mouth symptoms'.

Most of the intraoral and orofacial reactions were of chronic nature. The time associated with the referral procedure and travel to the unit made it unlikely that acute reactions were seen at the visit at the Unit. Acute reactions were usually handled locally (26, 27).

There is little information about systemic contact dermatitis in relation to dental materials. The most striking finding from the patch testing was the high frequency of positive reactions to gold. However, it should be considered that the present patients are selected in terms of complaints and presence of dental materials (28).

It might be difficult to assess the clinical relevance of patch-test results. Case reports support that there may be a beneficial effect of replacing dental materials containing the relevant substance, as has been shown in two patients documented earlier (28). It is our opinion, however, that patients with positive patch tests to gold in general do not need to replace gold-containing dental restorations except in cases where the patients also exhibit local intraoral reactions or skin reactions to, e.g. gold jewellery.

Widespread and unselected use of patch testing may not be clinically justified. A Norwegian board of dermatologists has issued guidelines for patch testing regarding dental materials: indications may be contact lesions in the oral mucosa, outbreak of otherwise unexplained eczema in association with dental treatment or clinically suspected contact allergy to a substance planned to be used in dental treatment (29).

A particular aspect is that the Norwegian National Insurance Scheme partly covers expenses to replace dental materials on certain indications. The first indication is in the case of direct contact lesion of 'lichenoid' nature, and the second is where a systemic contact dermatitis (remote reaction) can be assumed. The latter indication requires a statement from a dermatologist about the association between presence of the dental material and the reaction. In contrast to pharmacologic substances, the causality assessment of side-effects from dental restorative materials is difficult to make. Replacement of dental restorative materials is expensive and time consuming and causes discomfort, excessive loss of tooth substance, and sometimes pulpal complications (30).

Lack of information about composition of dental materials was a problem during the clinical evaluation. The manufacturers are not required to reveal detailed composition. The material safety data sheets are sometimes inaccurate (31).

When dealing with side-effects of dental materials, it is crucial to meet the patients with an open mind. The potential complexity of adverse effects from dental materials requires the combined efforts from several health disciplines. Our primary strategy is to suggest therapy for obvious medical or dental disorders, and to supply correct and updated information about adverse effects from dental biomaterials, both to the individual patient and to dental and medical practitioners.

The partly decentralized organization of the unit, where collection of information as well as prospective therapy takes place locally, works well. It is in fact a necessity in a country, like Norway, with a low population density.

New dental materials are continuously developed, marketed, and used (2, 32). Some of the new products may give rise to adverse effects of some sort. An adverse reaction unit could generate signals with regard to clinical reactions and diagnostics as well as being a resource base for the clinicians. A pre-requisite is that detailed compositional information is made available from the manufacturers.

The public is concerned about adverse effects from dental materials, as demonstrated by the amalgam controversy. Adverse reactions to materials used in dentistry span from localized, objective reactions to generalized ill-health where an association to the suspected material is difficult to establish. Potential biologic effects from dental biomaterials should not be overlooked, and there is a need for combined clinical and basic research in this field.

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