Side-effects of Dental Materials Reported in Scandinavian Countries

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Dental treatment usually involves a wide range of materials which continue to grow in number and complexity. During the last decade there has been an increasing demand for safety evaluation and control of dental materials. Since it is the members of the dental staff who handle the materials in their most reactive states they constitute the main risk category. Bearing this in mind reported side-effects in both patients and dental personnel in Scandinavia are presented. Data from the only two existing national registers for side-effects of dental materials, i.e. those in Norway and Sweden, are thus elucidated. Furthermore, recent mainly Scandinavian publications dealing with the side-effects of dental materials are presented. It can be concluded that a national register on the side-effects of dental materials, apart from revealing information regarding their frequency and nature, may detect changes in the profiles of adverse reactions and also serve as a tool for the post-marketing surveillance of dental materials.

Key words: dental materials, side-effects, adverse effects

INTRODUCTION

During the last decade there has been an increasing demand for safety evaluation and control of dental materials. The reason for this is that dental biomaterials are among the most extensively used materials for incorporation into the human body but it is also related to the fact that dental treatment usually involves a wide range of materials which continue to grow in number and complexity.

The frequency of adverse reactions to dental materials is considered low, 1:700-1:2600 in general practice but is probably higher in specialist practices. However, in this context it should be noted that in developed countries almost all individuals are exposed to dental materials. Thus considering the vast number of treatments provided many individuals may well be affected even if the frequency of adverse reactions is low.

In the literature the terms “adverse reactions”, “side-effects” and “unwanted effects” are often used synonymously. They can be described as unexpected or unusual events. In this context reactions caused by trauma or mechanical factors due to the presence of the material per se should be excluded.

Let us begin by considering the term “biocompatibility”, often defined as “com-
patibility between material and structure and function of the organism". This means that we are dealing with a reciprocal concept. Dental biomaterials in the oral cavity are exposed to a series of chemical and physical stresses such as pH-changes, thermal variations in the range 0-60°C, electrochemical processes, intermittent masticatory forces up to 100 N, abrasion and attrition forces. Such factors exert an influence on the materials and may cause the release of various degradation products which in turn may cause adverse reactions.

However, since it is the dental staff who handle the dental materials in their most reactive states it is important to note that it is this group which constitutes the main risk category. This is also reflected in many studies regarding adverse reactions to dental materials. Bearing this in mind, the purpose of the present work was to elucidate reported side-effects of dental materials in both patients and dental personnel in Scandinavia.

BASES FOR SURVEYING

Until 1993 there were no reporting systems intended to record the frequency and type of side effects associated with dental materials, on a national basis. However, in Norway in 1993 a Dental Biomaterials Adverse Reaction Unit, initiated by the Norwegian Board of Health and located in the University of Bergen began its activities. A few years later, in 1996, a similar national reporting system was implemented by the National Board of Health and Welfare in Sweden. This unit was set up at Umeå University, Department of Dental Materials Science. The intention was to try to clarify the frequency and nature of adverse reactions related to dental materials.

Reporting is voluntary and licensed dentists and physicians, and in Sweden also licensed dental hygienists are expected to send in the forms. In both Norway and Sweden a form specially designed for this purpose is used for reporting adverse reactions.

Many of the materials within the still increasing range that is used in modern dental care have a highly complex composition and structure and can clearly be sensitive to technology. It is therefore very important that even cases where the connection between material and undesired reaction is doubtful are reported. These cases may come to constitute an important warning marker in future reports concerning similar cases. Therefore, when the reporting systems were initiated the professionals concerned were requested to report reactions even where there was doubt about the association between the reaction and the material(s).


In evaluating the connection between material and side-effects, medical experts are consulted where appropriate, mainly in the fields of occupational and environmental health medicine and dermatology. In Sweden the category descriptions used are Probable, Possible, Uncertain and Unclassifiable. The criteria are modified WHO definitions related to suspected side-effects of pharmaceutical products, and have been
co-ordinated with corresponding criteria used in the Norwegian register.

Besides data from the two existing national registers on side-effects of dental materials also results from current, mainly Scandinavian, publications will be presented.

RESULTS OF SURVEYING

Reports concerning patients
Among the patients the most common age groups were 50-59 years in Sweden and 40-49 years in Norway. There were about twice as many women involved in adverse reaction reports than men. In approximately 25% of the patients the odontological or medical staff were the first to notice the reaction, i.e. the patient was probably unaware of it7).

In some cases, for natural reasons, the reporter had indicated more than one suspected cause of the side-effects. In most cases, about 65%, the side-effects were seen as related to fillings, i.e. to materials and the procedures associated with them. In these cases, when intraoral findings/symptoms were present, both reporters and patients considered that most of the reactions were related to dental amalgam and in

Fig. 1 Lichenoid oral mucosal reaction related to an amalgam restoration.
the remaining cases to composites and/or dentin bonding materials. After materials for fillings, materials for fixed prosthetic restorations, mainly the metallic materials, were most often seen as being associated with the side-effects.

Objective intra-oral findings were reported in about half the cases. The most common findings were local reactions, for example so-called lichenoid reactions, i.e. white or red lesions in the mucous membranes where they came into contact with dental restorations (Fig. 1). Such reactions should be reported although their etiology is debatable. Erythema, erosions/blisters and swellings/oedema are also reported. There were few reports concerning the surrounding tissues but among these the occurrence of problems related to temporo-mandibular joints and/or masticatory muscles were fairly common. If one looks at intra-oral problems reported by patients themselves, there is a predominance of stinging, burning sensations, pain and tenderness. A stinging, burning sensation was also a common symptom from the lips, face and jaws, and apart from this, the most common reports were of skin irritations. When "burning mouth symptoms" with local pain and discomfort were reported there were in some cases indications that there was a relationship between the symptoms and the material, for example hypersensitivity to a constituent of a dental material present in the oral cavity of the patient concerned.

With regard to the distribution of the patients' reported general symptoms, the spread was largely even and these symptoms were often judged by the patients themselves, and sometimes also by the reporter, as being related to the presence of amalgam fillings. In some cases it was also considered feasible that the reported symptoms might be the side-effects of medicines which the patients in questions were taking. However, it is clear that general symptoms which are reported as being related to the presence of, or earlier exposure to, dental amalgam are often part of a complex and non-specific pattern of symptoms, including muscle and joint pains, fatigue, headaches and skin and respiratory tract problems.

In a review article by Hensten-Pettersen (1992) on the side-effects of dental casting alloys it was pointed out that allergic reactions to gold based restorations seem to be reported more often than allergic reactions to dental alloys containing nickel. Possible allergic reactions to gold were reported by Stenman and Bergman. In a later study by Björkner et al (1994) it was suggested that a positive skin test to gold sodium thiosulfate represents gold allergy. Furthermore, it was pointed out that in routinely patch-tested dermatitis patients at the same department, gold sodium thiosulfate was the second most common sensitizer. In most patients it was difficult to explain the source of sensitization to gold or to see its clinical relevance. However, a study by Bruze et al (1994) aimed to elucidate the clinical relevance of contact allergy to gold sodium thiosulfate. The results showed that gold allergy was overrepresented in those who had dental gold in their mouths. In people with contact allergy to gold a dermatitis on the ears, fingers or eye area was most frequent. The authors concluded that exposure to gold jewelry and to dental gold may be important in the sensitization and elicitation of dermatitis.

Denmark and Finland have no national registers for the side-effects of dental ma-
materials. However, in an interesting publication Kerosuo et al (1996) studied the frequency of nickel allergy in relation to orthodontic treatment and the piercing of ears\textsuperscript{15}. The subjects were 700 Finnish adolescents (14-18 years) of whom 68\% had a history of orthodontic treatment with metallic appliances. It was found that orthodontic treatment did not seem to affect the prevalence of nickel sensitization. None of the girls who were treated with fixed orthodontic appliances before ear piercing showed hypersensitivity to nickel, whereas 35\% of the girls who had experienced ear piercing before the onset of orthodontic treatment were sensitized to nickel. The data suggests that treatment with nickel-containing metallic orthodontic appliances before sensitization to nickel (ear piercing) may have reduced the frequency of nickel hypersensitivity.

Reports concerning personnel

Reactions to dental materials which affect dental personnel in their professional activities, often called occupational reactions, are also sent in and recorded in the two national side-effects registers. However in the Norwegian register only a few reports have been received since its start in 1993, while in Sweden 163 reports were received during the three years from 1996. Considering the number of dentists working during the periods concerned, i.e. about 4300 in Norway and about 8800 in Sweden, the difference in the number of reports concerning dental personnel is not easily explained but it may be related to the way the reporting procedures were introduced to the practitioners\textsuperscript{7,16,17}.

The most common age group among the 163 Swedish cases was 40-49 years. This included 76 dentists, half of whom were women, and 87 female dental assistants (nurses) or hygienists. The predominant symptoms reported among dental personnel were skin problems but to a small extent also problems related to eyes and the respiratory tract. The vast majority of these symptoms were associated with resin based materials, i.e. composites and the bonding materials used with them. Most of the skin reactions had been dermatologically investigated and hypersensitivity to one or more of the acrylic monomers was often verified. In addition skin problems were often related to the use of gloves in professional activities. Only 4\% of the cases were considered possibly related to dental amalgam.

As previously pointed out there are no national registers for the side-effects of dental materials in Denmark and Finland. However, in a publication using data from a questionnaire survey among dentists in Denmark it was revealed that diagnosed allergic eczema caused by (di)methacrylate containing materials was reported in 0.7\% and by latex in 0.6\%.\textsuperscript{18} Furthermore, based on the description of symptoms the authors point out that the figure may be as high as 2\% for allergy to methacrylates and that figure may also be valid for allergy to latex.

Apart from this it seems important to mention that as early as 1990 Munksgaard et al published data on 8 dentists and one dental nurse who had developed dermatologically verified allergic contact dermatitis caused by exposure to (di)methacrylates, especially those found in resins, in dentin bonding agents, in rebasing
materials and in other prosthetic materials\textsuperscript{19}). The eczema was characterized by location on the first, second and third finger of the left hand showing redness, desquamation, fissuring and excoriations. Skin patch testing with various test substances revealed positive reactions to EGDMA in 8 cases. It was suggested that this reaction was a cross-reaction and that the sensibilization was caused by MMA, TEGDMA, HEMA and/or BUDMA. One of the dentists had to give up practicing.

Mürer \textit{et al} in Denmark (1995) also published a study which revealed a rapid increase in skin problems among dental technician trainees working with acrylates\textsuperscript{20}). Preventive actions were called for, e.g. increased use of encapsulated systems, use of gloves with a well documented protective effect and mandatory courses on the hazardous effects of dental materials. In another Danish study\textsuperscript{21}) on “Methylmethacrylate and organic dementia” it was concluded that the results support the hypothesis that symptoms of organic dementia may be connected to exposure to MMA. Acute and chronic damage to the central nervous system occurs, even with exposure below the safety limit and therefore the occupational environment of dental technicians, including the current safety limits, should be revised.

Jacobsen and Hensten-Pettersen in Norway (1995) published data on occupational health problems among Norwegian dental hygienists\textsuperscript{22}). Among chemically induced health problems the most frequent complaint was dermatoses of hands and fingers (37%), caused by various chemical, work-related factors. Latex gloves were responsible for 1/3 of these reactions.

In Finland the general register for occupational disease has revealed\textsuperscript{23}) that for dental personnel there was a remarkable increase in reported skin reactions from 1982 to 1994. Currently Finnish dentists have the highest risk and dental nurses have the 4\textsuperscript{th} highest risk of any occupation of developing occupational allergic contact dermatitis. The risk was 6.4-fold in dentists and 6.1-fold in dental nurses, compared to the general working population. The authors point out that it is evident that safer acrylics and protective gloves, better product declarations and material safety sheets, as well as more information about protective measures, including non-touch working techniques are needed.

The apparent variations between the Scandinavian countries regarding reported occupational reactions to dental materials among dental personnel may be related to different reporting methods/systems, to different occurrences of reactions or to differences in practice and education.

\textit{Estrogenicity of certain composites}

Although reports on any side-effects related to estrogenicity of certain resin based dental products have not occurred in Scandinavia this item has been discussed in a couple of interesting publications by, among others, a Swedish author, Professor Karl-Johan Söderholm, University of Gainesville, Florida. It might therefore be of interest to comment briefly on what has been discussed in Scandinavia.

Initially there was a Spanish publication from the university of Granada which drew attention to the effects of a dental sealant based on bis-GMA\textsuperscript{24}). Samples of sa-
liva from 18 people who had had the sealant (50 mg) applied to 12 molars were collected 1 hr before and 1 hr after this treatment. Bisphenol-A was identified only in saliva collected after treatment. Diluted saliva samples were used for cell culture tests with human breast cancer cells. It was shown that degradation products/contaminants from the bis-GMA based sealant altered the proliferative nature of the cells which turned out to grow faster with saliva taken after than before treatment.

In a subsequent study by Mariotti, Soderholm and Johnson (1998) adult, female Swiss-Webster mice were ovariectomized and received either oil, estradiol (100 μg/kg) or one of two bis-GMA doses (25 μg/kg or 100 μg/kg). Starting on the day of surgery, the hormone, drug or oil was injected subcutaneously 3 times a week. After 3 weeks, the animals were sacrificed, the uteri removed, weighed and stored at −80°C for biochemical analysis. The results of the biochemical analyses of the uterine tissues revealed that estradiol resulted in the maintenance of DNA content, RNA content and RNA/DNA ratios significantly above the ovariectomized controls while neither the low nor the high doses of bis-GMA stimulated RNA content, DNA content or RNA/DNA ratios above ovariectomized controls. However, both estradiol and the high dose of bis-GMA caused a significant increase, above ovariectomized controls, in uterine collagen content.

In a further publication by Soderholm and Mariotti (1999) the authors critically surveyed research dealing with the release of resin components from dental composites and the potential of these agents to mimic or disrupt estrogenic cell responses. These studies included those on synthetic methods used to make bisphenol-A glycidyl methacrylate, or BIS-GMA, and the biological effects of this resin in cell culture and animals. The estrogenic effect of bisphenol-A was targeted because bisphenol-A is present as an impurity in some resins and as a degradation product from other resins. The review revealed that short-term administration of BIS-GMA and/or bisphenol-A in animals or cell cultures can induce changes in estrogen sensitive organs or cells. However, the authors considering the dosages and routes of administration as well as the modest response of estrogen-sensitive target organs, conclude that the short-term risk of estrogenic effects from treatments using bisphenol-A based resins is insignificant while long-term effects need to be investigated further.

**DISCUSSION**

The complexities of analyzing reports on adverse reactions from dental materials have undoubtedly contributed to the absence of reliable data concerning the frequency and nature of such reactions. In this context it should be pointed out that the side-effects of dental materials may have the same pathogenic mechanisms in patients and personnel. Some of these are based on the reinforcing effect of the immunological system while the mechanisms of others are not so well known.

The amounts of substances released from dental materials within the oral cavity are usually too low to cause systemic toxic effects. However, many of the products used in dentistry are irritating and may cause local damage. Thus, by reducing the
natural barrier effect, an irritative contact mucositis due to contact with irritating substances may occur. In reactions mediated via the amplifying mechanisms of the immune system, small amounts may also lead to clinical manifestations of allergic contact dermatitis and urticaria. As regards reactions, for example skin problems, occurring orofacially or elsewhere on the body, skin-patch testing, based on relevant indications, may in some cases reveal hypersensitivity to one or more of the constituents of the dental materials present in the oral cavity of the patient concerned. Occupational adverse reactions, especially the development of an allergy to constituents of the resin-based materials and adhesives, have emerged as a serious problem.

It seems clear that, in order to be able to clarify the frequency and nature of side-effects related to dental materials in a systematic and comprehensive way, it is desirable to make the reporting of such side-effects compulsory. This should be a natural and important part of the quality control system of the dental care sector. Accordingly the Swedish National Board of Health and Welfare intends to make a proposal to the Ministry of Health and Social Affairs that the reporting be made compulsory through a special statute, and that the civil registration number of people named in reports should be used within the register\textsuperscript{17}.

Furthermore, a national register on the side-effects of dental materials may detect changes in the profiles of such reactions at an early stage. Harmonization of data collected in several countries will admit a broadening of the data base, thereby also providing a tool for post-marketing surveillance of dental materials. It is also worth mentioning that at present discussions intended to introduce the national registration of side-effects of dental materials are underway in a couple of other European countries, apart from Norway and Sweden. The World Health Organization has urged other countries to start similar projects and will coordinate their efforts on a global basis and produce reports as needed\textsuperscript{27}. Considering the fact that the majority of the population is exposed to dental materials, it is important that the reporting of side-effects be as complete as possible.

It seems appropriate to remember the foresight of the late Professor Gunnar Ryge, originating from Denmark, who already in 1961 emphasized: “the obligation on the dental materials researcher to widen his sights to acknowledge and include the biological and clinical aspects”\textsuperscript{28}.

REFERENCES

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