



Biocompatibility of materials and products used in medicine and dental medicine

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Abstract

Background

Biomaterials are defined as substances intended to replace a part of the body or its function in a secure, safe and economical way, while being physiologically and aesthetically acceptable. Biomaterials can be bioinert or regenerative. Biocompatibility refers to the ability of a material to elicit a specific biological response after administration in a living organism. Measuring the biocompatibility of materials used in dentistry is not an easily achievable task.

Methods

Scientific databases – PubMed, Scopus and Medline, as well as monographs, textbooks on the topic, websites were used to search for the data required. The following keywords were used: biomaterials, biocompatibility, dental medicine, medicine, toxicity.

The aim of the following article is to summarize the main conclusions authors in the field have reached to when discussing biocompatibility and tolerance of material and products used in medicine and dental medicine.

Results and discussion

In depth results and discussion are presented in the section. Materials used in medicine and dental medicine encompass a wide range of compounds, with different chemical and physical structures. Therefore, profound knowledge is needed to be able to treat the patients and keep them safe as much as possible from possible adverse biological reactions.

Conclusions

Medical and dental specialists should pay special attention to the content of the materials they implement in their treatment plans on a daily basis. Being profoundly informed on the general diseases, medications usage and allergic status of their patients can prevent adverse complications. Although medicine explores and studies in depth possible biological reactions, still they may occur.

Key words: biomaterials, biocompatibility, dental medicine, medicine, toxicity

Background

Biomaterials are defined as substances intended to replace a part of the body or its function in a secure, safe and economical way, while being physiologically and aesthetically acceptable. They are made from natural or synthetic substances. According to the European Society for Biomaterials, a biomaterial is defined as: a material that contacts a biological system for the purpose of evaluating, treating, improving, or replacing a specific tissue, organ, or body function. (1, 2, 5)

Biomaterials can be bioinert or regenerative. The contact between the biomaterial and a given cell, tissue or living material takes place through a special interface – a structure that forms the border between the material and the living organism. The reactions that will occur at this boundary also determine the fate of the biomaterial after the healing process. (1, 2, 3, 5)

According to theoretical data, biocompatible materials are divided into three main groups: biotolerant, bioinert (biopassive) and bioactive. Biotolerant materials release substances in non-toxic concentrations, bioinert materials do not release toxic substances, but do not show a positive interaction with living tissues. Bioactive materials show proven active interaction with body tissues. Incompatible are those materials that release substances in the body in toxic concentrations and/or have the ability to trigger an immune response that varies from mild allergic reactions to serious ones, including

processes leading to systemic disorders. Biomaterials are also the tissue repair (bone repair) materials used in dentistry (oral surgery, dental implantology). These are: tissues, biomaterials or their combination, placed in the receiving surgical area, to support the regeneration of the tissues, to preserve or restore their volume and qualities. (1, 2, 3, 4)

Biocompatibility refers to the ability of a material to elicit a specific biological response after administration in a living organism. The concept does not define only one quality of the material, but reflects complex interactions with the biological environment in which it is placed.

In 2008, Williams defined biocompatibility as: „the property of a biomaterial to perform its intended function in relation to an assigned medical therapy without causing the manifestation of undesirable local or systemic reactions in the recipient of the therapy, but helping to achieve the most appropriate clinical or tissue response as appropriate.” (2)

Over time, the definition of the concept of biocompatibility gradually changed from containing the phrase „lack of toxicity“, through „lack of cytotoxicity“, to „good tissue tolerance“, „lack of genotoxicity“, „lack of mutagenicity“, to arrive at „creating suitable conditions for tissue recovery“. The implanted biomaterial must induce an appropriate response from the body, which means no thrombus formation, no bacterial growth and a healing process. It is important that the material does not cause an unwanted response from the body, which can end in a complication or its rejection. Therefore, the body's response to the implanted biomaterial must be evaluated. (2, 5, 6, 7, 18)

The implantation of a biomaterial in the body is followed by several logical responses from the body: as a result of the injury and blood flow, primary interactions between the blood and the material and protein adsorption are established; primary matrix is released at the interface between material and tissue; then a process of acute inflammation follows (polymorphonuclear leukocytes, monocytes and fibroblasts are directed to the site of damage), which if it does not take the path of proper healing (i.e. if the inflammatory process, due to the too great trauma during implantation, is very strong), is accompanied by a process of chronic inflammation and formation of granulation tissues (foreign body type reaction, presence of giant cells of „foreign body“ type – actually fused macrophages, differentiated from monocytes at a later stage) – the material is

surrounded by a fibrous capsule, is not incorporated into the body and is rejected by it. (2, 3)

The latest conclusion reached by the scientists is that it is possible to modify the reactions of the material-tissue interface. Therefore, several factors must be taken into account when considering the biological response. The most important of them include: location of the material, duration of presence of the material in the body (contact with the internal environment of the organism), subjecting the material to functional stress, changing the surface of the material, selection of inert material. (2, 5, 6, 7, 18)

Methods

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The aim of the following article is to summarize the main conclusions authors in the field have reached to when discussing biocompatibility and tolerance of material and products used in medicine and dental medicine.

Results and discussion

Measuring the biocompatibility of materials used in dentistry is not an easily achievable task. Measurement methods are constantly evolving as more is known about the interactions between dental materials and oral tissues. The evaluation of the biocompatibility of dental materials is a difficult and responsible task, since a variety of adverse tissue reactions are known. Clinicians must remember that there are no completely inert materials. When a material is placed in living tissue, interactions between it and the tissue always exist, and from these the biological response originates. A satisfactory response for dental purposes is the absence of a response from the body, which may be systemic or local. (2, 7, 8)

Initially, the new materials were placed in the patient's body to test whether or not they were biocompatible. However, this has not been practiced for many years, and current materials undergo rigorous biocompatibility testing before being administered to humans. Nowadays, the approach to testing the biocompatibility of a material is to start with in vit-



ro tests, most often on cell cultures. If these studies give promising results, then animal studies (in vivo tests) are carried out. The final stage of the tests are the clinical trials. Biocompatibility is measured by: in vitro tests; in vivo tests; usage tests. (2)

In vitro tests are conducted outside the human body, aiming to simulate the biological reactions to the given test substances in contact with the oral environment.

In vivo tests are conducted by implanting the materials into animals. Clinical and observational studies, as well as animal studies, mostly on large animals such as primates and dogs, are used to further investigate the potential harm that the biomaterial may cause to the patient or dental staff. Animal models are best, but they are relatively expensive, time-consuming and involve ethical issues. It is sometimes difficult to control certain factors, unlike in vitro tests. In vivo studies, however, most adequately simulate the use of the material in patients (usage tests). (2, 8)

It is a fact that currently on the market, fully regulated, materials are found that have not actually been tested for their biocompatibility, if their composition, sterilization method, production method and method of contact with the body are close and analogous to already known, tested material. (2)

Biocompatibility of restorative, cementing and lining materials containing resins. The mentioned materials are widely used in the practice of physicians in medicine and dental medicine nowadays, as they have excellent mechanical, technological, manipulative and aesthetic qualities. These include, for example, composite restorative materials (including those reinforced with fibers), resin-modified glass-ionomer cements, compomer materials (composite materials with added inorganic fillers and acids similar to those in glass-ionomer cements), various adhesives, photopolymerizing calcium hydroxide cements, etc. However, concerns about their biocompatibility remain. These materials contain an inorganic (filler) and an organic polymer component, the latter being the perilous one. It is a highly cross-linked polymer matrix obtained as a result of addition polymerization of individual molecules. Some authors define these substances as resins. The presence of residual monomers is known, with insufficient degree of conversion during the polymerization. In other words, the amount of non-polymerized dimethacrylates and methyl-meth-

acrylate monomers is above a certain percentage tolerated by the body. They have a pronounced cytotoxic effect and can cause allergic reactions in patients on the one hand, but also in clinicians if gloves are not used. Unpolymerized molecules are dissolved in saliva, and hydrolytic dissolution and imbibition result in release of monomers. According to scientists, some of these ingredients can change the endocrine and hormonal balance of the body. The mechanical properties of poorly polymerized material are also strongly negatively affected. Allergic reactions can be local, but systemic reactions are also known, often far from the site of contact. The toxicity of resins in direct contact with fibroblast cells has been demonstrated in cell culture studies. In general, acrylate compounds are more toxic than methacrylates, as a hydroxyl group in the monomer enhances cytotoxicity. Dimethacrylate compounds, the most familiar of which are bis-GMA (bisphenol A-glycidyl methacrylate) and urethane dimethacrylate (UDMA), are more toxic than monoacrylates. Composite materials that are less filled, i.e. have more organic component and less inorganic (fillers), are more toxic, with lower biological tolerance. It is not advisable to place these materials without an isolating first in the treatment of deep carious lesions, due to the direct possibility of damage to the adjacent pulp. Hydroxyethyl methacrylate (HEMA), a hydrophilic monomer with a small molecule and low molecular weight, easily penetrating the dentine tubules, has been shown to be the most damaging substance released in resin-modified glass ionomer cements. It can cause reactions from pulp inflammation to allergic contact dermatitis. Although these cements are often used, they will not have the same biocompatibility as conventional glass ionomer cements. Like all polymer cements, resin-modified ones biodegrade under oral conditions and are highly soluble in water. (9-17, 19)

Biocompatibility of dental cements. Dental cements are basic clinical obturation materials, with relatively low mechanical but high medico-biological qualities. They are generally divided into temporary and permanent. The latter, according to their purpose, are divided into: for fixing prosthetic structures (luting), for bases and insulations (base and liners, lining cements) and restorative (for making obturation, restorative). Other authors add to these three main groups a fourth – cements for

prophylactic obturation of deep fissures in permanent and temporary children's teeth. According to the origin of their ingredients, cements are divided into mineral, organic-mineral and organic. According to the type of hardening reaction, they are divided into those with an acid-base reaction, those with a polymerization reaction (polymer cements) and a relatively new group – hybrid cements, in which there is a main hardening reaction to which a secondary one is grafted. Acid-base and polymerization reactions can affect the biocompatibility of these materials. (6, 7, 19, 20, 23)

Temporary cements are used for temporary cementation of temporary prosthetic structures until the final one is made or for temporary cementation of permanent prosthetic structures to evaluate their qualities and treatment success. There are generally 2 groups available on the market – eugenol-containing and eugenol-free temporary cements. Care must be taken with eugenol-containing ones, because if a composite cement is subsequently used – eugenol inhibits the polymerization of composites, composite cements and resin-modified materials. Eugenol does not affect the hardening of cements with acid-base reaction. Furthermore, eugenol can penetrate the dentine tubules. It has known healing properties on the pulp of the tooth if there is at least 0.75mm of dentin above it. Otherwise, with less tissue, eugenol acts as an irritant and may even cause pulp necrosis. Therefore, the biocompatibility of eugenol should be well evaluated considering that the distance to the pulp can be subjectively estimated. From a practical point of view, if a composite or resin-modified cement is to be used to fixate the final prosthetic structure, it is best to use a eugenol-free provisional cement to fixate the dental prosthesis. (7, 19, 24, 25)

Among the representatives of the permanent cements, zinc-phosphate cement, used for nearly 150 years and still considered the „gold standard“ by some authors, due to the appropriate cementing layer, good mechanical properties, low solubility in oral fluids, wide indications for use, are hardened by means of an acid-base reaction between a powder containing zinc and magnesium oxide and a liquid – an aqueous solution of phosphoric acid. The pH of the resulting solution drops to 2, which represents strong acidity. Moreover, the interaction reaction is highly exothermic. These two properties, combined with the hydraulic pressure that is created when cementing the fixed prosthetic structure

and the possible low amount of dentin between the cement layer and the pulp tissue, can lead to a hypersensitivity reaction and even necrosis of the tissue, due to microscopic but sufficient penetration of some of the cement (actually unreacted phosphoric acid, due to a faulty technique of not adding enough powder during mixing) in the dentinal tubules. (7, 20, 23, 25)

Zinc-polycarboxylate cement is mixed with a powdered ingredient similar to that of zinc-phosphate (with some additives), but the liquid is an aqueous solution of polyacrylic acid. The reaction is again acid-base, the pH again drops to low values. However, the molecules of acrylic acid are significantly larger than those of phosphoric acid and would therefore be difficult to penetrate through the dentinal tubules and, accordingly, cause sensitivity. Polycarboxylate cement, unlike zinc-phosphate cement, forms a chemical bond with tooth structures due to chelate bonds with Ca^{2+} ions – according to scientists, this prevents the micro-infiltration of bacteria and their metabolites and protects the pulp from inflammation. (7, 19, 20, 22)

Glass-ionomer cements are mixed with powder consisting of calcium-aluminum-fluorine-silicate glass and a liquid – a solution of polyacrylic or copolymers – tartaric, maleic, itaconic, etc. acids. Cement can serve as a depot for fluoride ions, which have a certain remineralizing effect on hard tooth tissues. The glass-ionomer cement also binds chemically to tooth tissues due to chelate bonds being formed. The molecules of the organic acids in the composition are large and no seepage into the tubules is observed. However, there have been reports of post-operative sensitivity that does not subside with time. Some scientists believe that due to the hydraulic pressure that is created when cementing, a possible low amount of dental tissues next to the pulp and the increased concentration of fluoride ions in this cement, cause the pain. It is known that, in certain concentrations, fluorine acts favorably and stimulates the secretory activity of ameloblasts to release matrix, which matures and mineralizes subsequently. Above certain concentrations, however, fluoride is a proven irritant and can have a toxic effect on ameloblasts. In order to avoid all possible biological consequences for the dental tissues, there must be sufficient preserved pulp tissue, time must be allowed for tissue regeneration from the trauma of the preparation, the cement must be mixed mechanically and the proportions must be



meticulously observed (which also applies to polycarboxylate cements), to isolate tissues well during cementation and afterwards, due to the known high sensitivity of cement during the hardening process to excess humidity and dryness of the environment. (7, 19, 20, 21)

Scientists have established the positive properties of a relatively new cement, a water-based composition consisting of calcium aluminate and the components of glass-ionomer cement, mixing with distilled water. The curing reaction is acid-base. Bioactive properties are present. Immediately after mixing, the pH is 4, reaching alkaline values of 8 after a few hours, unlike other cements with an acid-base hardening reaction. Apatite crystals are synthesized in contact with phosphate solutions (e.g. saliva). They are incorporated between the cemented structure and the tooth tissues, sealing the gap and preventing microleakage and the possibility of caries. Moreover, the material creates an excess of calcium ions, which further creates conditions for successful remineralization of dental tissues. These ions stimulate the conversion of preodontoblast cells into odontoblasts, leading to the synthesis of secondary, reparative dentin. The cement also has the ability to emit fluoride ions, comparable to conventional glass ionomer cements. Apatite crystals resistant to bacterial acid attack are created and the main mechanism for the development of dental caries is prevented. No postoperative tenderness is reported. This cement, together with the polycarboxylate cements, are the least irritating cements on the market, with clearly expressed positive bioactive qualities. (7, 19, 30)

Biocompatibility of materials used in treatment, restoration and regeneration of oral hard and soft tissues (Ca(OH)₂, MTA, Emdogain). The ideal material used for the mentioned purposes should be biocompatible. Medical and dental practitioners have a vast resource of materials at their disposal, but few of them are non-toxic and compatible for the use in the oral cavity or human organism, let alone for direct contact with, for example, the dental pulp when treating pulp inflammation. Materials that are most compatible with oral hard and soft tissues are usually those that are most stable, physically inert, and do not cause inflammatory tissue changes or pain. They do not allow the release of toxic substances in the tissues. Several types of biomaterials are known on the market, used for

regeneration of hard dental tissues, treatment of perforations, guided tissue and bone regeneration (GBR, GTR). Their task is to prevent micro-leakage in the direction of the dental pulp, to induce the synthesis of growth factors, as well as to activate the stem and local repair cells to start the process of restoring the damaged tissues. (26-29)

Typically, biomaterials that are used for tissue regeneration are not used for the definitive restoration of lost hard dental tissues. Most hard and soft tissue regeneration procedures require the removal of non-vital tissue and disinfection prior to placement of the regenerative material. Dentists usually use dilute sodium hypochlorite and chlorhexidine solutions for root canal irrigation. Contact with vital tissues should be avoided whenever possible, as most disinfectants used in medical procedures have cytotoxic properties to living tissues. In general, all dental adhesives, composites, sealers, conditioners, modified glass-ionomer cements, amalgam, zinc-oxy eugenol materials are cytotoxic and should not be placed in contact with living structures. Zinc-oxy-eugenol materials are considered the most toxic, with the lowest biocompatibility – any material that is more toxic does not have the necessary biocompatibility. It is important to know that the greater the amount of dentin between the pulp and the placed materials, the smaller the possibility of penetration of cytotoxic substances to the pulp tissue. Of course, modern techniques for minimal invasiveness of the treatment, maximum preservation of living tissues, avoiding overheating of the tissues, i.e. using adequate amount and well-directed cooling, etc., must be observed. On the other hand, certain materials, such as calcium hydroxide, tricalcium silicate cements, which include mineral trioxide aggregate (MTA) and Biodentine, are usually placed in direct contact with the living pulp to carry out regeneration processes in direct pulp capping, various pulpotomy procedures, apexogenesis, etc., used in children's dentistry, and also in the treatment of root perforations. These materials, although highly biocompatible, do not have the mechanical properties to permanently restore the tooth. MTA overtakes calcium hydroxide as the best choice for placing a material in direct contact with exposed pulp tissue to perform a procedure to stimulate the formation of secondary dentin. MTA has very low toxicity, good sealing properties, stimulates the release of growth factors that support healing. Calcium hydroxide also

stimulates the formation of a dentine bridge over the exposed pulp tissue, but its solutions are highly alkaline – although they act as extremely strong disinfectants, they necrotize the tissues. It is good to remember that just as there is no biomaterial to which the body does not have some reaction, there is no biomaterial that can provide 100% recovery of damaged cells and tissues. MTA is currently doing the best on a global scale. Scientists continue to develop its properties to improve its biocompatibility and sustainability. (26-30)

Biocompatibility of dental amalgam. Dental amalgam is a cheap and well-known restorative material to dentists, with good manipulation qualities, dating back to the 19th century. It is obtained by vigorous manual or mechanical mixing (trituration) of spherical metal shavings containing silver, tin, copper, etc. elements (solid phase) and liquid phase – mercury. A number of modifications to amalgam ingredients have been made over the years, including, in the latest generations, amalgams-containing copper (to reduce the gamma-2 phase, greatly improving mechanical properties and corrosion resistance), mercury-free ones (containing liquid phase of gallium), as well as containing fluorine compounds for caries protective action. (30, 31-36)

The concerns of scientists about the adverse effects of mercury in amalgam on the health of patients and staff in dental clinics are known. Mercury is a highly toxic metal, a typical representative of cumulative toxins. Liquid mercury without an oxide layer evaporates quickly, especially when the temperature rises. Exposure to high levels of mercury vapor adversely affects the kidneys, brain and nervous system. There is a special danger for pregnant women and small children – the probability of developing cerebral palsy, deafness, blindness increases. In adults, chronic poisoning leads to memory loss, tremors, loss of vision. Allergic reactions of some patients to amalgam fillings are known. A number of scientific studies point to a connection between mercury poisoning and cases of autism, autoimmune diseases, gluten enteropathy, etc. Metal ions can be released from the obturation, some of which are resorbed with the saliva, and another part – through the oral mucosa. Patients with dental amalgam fillings and other metallic prosthetic structures often suffer from pathogalvanism due to corrosion. The toxicity of amalgam is also due to it. (31-37)

However, according to other scientists, there is no evidence of a link between mercury from amalgam fillings and public health problems, since the amount of mercury released from these restorations during their fabrication or removal is considered to be far less than when ingested through food (fish and seafood), the water or in other ways. According to the USA FDA (2015), dental amalgam is safe for use in adults and children over 6 years of age, and the amounts of mercury in blood, plasma, saliva, breast milk, hair, brain tissue and liver are far below the dangerous limits. However, taking precautions is a must. The fact that dental personnel and patients are differently exposed to mercury must also be taken into account. It has also been shown that the use of good aspiration, water spray and rubber dams when removing such fillings or when shaping and polishing already made ones significantly reduces the chance of the patient ingesting amalgam particles and the patient and dentist being exposed to inhalation of mercury vapor. Dental offices where amalgam fillings are removed must be equipped with amalgam separators to prevent amalgam particles from entering the sewers – one of the main routes for mercury contamination of the environment. To resort to the use of ready-to-use capsules, with factory-dosed ingredients (mercury and metal shavings), which are activated and mixed on the spot – thus minimizing the harmful effects of mercury. Residues should be carefully collected and stored in containers under water and never disposed of with household or hazardous biological waste. Companies have been established that deal with the disposal of amalgam residues. The floor of the dental office should be smooth, so that mercury does not remain there in the event of an accidental spill. Mercury is easily neutralized by a well-known method with powdered sulfur – stable at room temperature and insoluble in water mercuric sulfide is formed. The dental office should be ventilated frequently, as well as checks of the concentration of mercury vapor in the air, and for those working – to examine the concentration of mercury in the blood. The ventilation in the working rooms should have suitable filters and negative pressure. (7, 30, 35-38)

Biocompatibility of oral hygiene products and dental adhesives. A huge variety of oral hygiene products are available on the market – those for mechanical and chemical combat with oral plaque biofilm (dental plaque). It is an etiological factor



for the development of carious lesions and gingival inflammations (most often plaque-induced gingivitis). The first lead to a number of complications of dental caries, such as inflammation of the pulp – pulpitis, and in more severe cases to inflammation of the periapical bone. Gingivitis can develop into periodontitis, which are plaque-induced inflammatory diseases of the periodontium, accompanied by bone loss. A condition that inevitably leads to tooth loss if not timely treated. (38, 39)

Tooth pastes and flosses, washing solutions, whitening products, dental adhesives for complete dentures are known in the mentioned group of means. All of them have certain biological properties that must be known, since local and systemic reactions to them are studied, even though their contact with oral tissues is too short. There are fewer scientific studies on the biocompatibility of these products compared to studies on their efficacy, precisely because of the short contact with the tissues in the oral cavity. Biological hypersensitivity reactions to some of the components of oral hygiene products have been found, ranging from contact dermatitis to anaphylactic reactions. Patients should be instructed very carefully how to use these products and their compliance should be monitored. It should be considered which patients are predisposed to the development of the unwanted side effects of the substances or belong to risk groups (patients with known allergies, patients suffering from dry mouth, young children, pregnant women, patients on chemotherapy or radiotherapy). Dental and medical professionals should inform the authorities if such reactions are observed. More studies are needed on the biocompatibility of the cited products, without stopping their development in the direction of clinical effectiveness and biological compatibility. (38, 39, 45)

Toothpastes contain quite a number of different substances – water, abrasives (aluminum hydroxide, calcium hydrogen phosphate, carbonate, silicon and hydroxylapatite particles), fluorides (mainly in doses of 1450 ppm, while those with a smaller amount of fluoride are also sold – children's; fluorides are usually in the form of sodium fluoride, with newer forms containing stannous fluoride and sodium monofluorophosphate), detergents (mainly sodium lauryl sulfate), antibacterial agents (triclosan, zinc chloride), flavoring agents, remineralizing agents (such as hydroxylapatite nanoparticles and calcium phosphate), humectants (glycerol, sorbitol,

polyethylene, and propylene glycol), desensitizers (strontium chloride, arginine, potassium nitrate), zinc citrate, and sodium polyphosphate, which suppress tartar formation. It is important to emphasize that commercial formulas do not contain absolutely all of the listed substances. (45)

As far as the biocompatibility of toothpastes is concerned, reactions from the body have been found mainly for the following ingredients of the various formulas: fluorides, sodium lauryl sulphate (SLS) and triclosan. (46-52)

Fluoride is naturally found in all water resources, but not in the same concentration – in drinking tap water the concentration can be low, while in bottled mineral water – it can be high. According to the ADA, the optimal dose of fluoride in drinking water is 0.7 ppm or 0.7 mg/L. Therefore, in areas with a low fluoride content in the drinking water, it can be additionally fluoridated to the optimum dose. A number of scientific studies indicate that even in the time of wide access to fluoridated toothpastes, various fluoride additives, varnishes and gels for professional use, etc. fluoride in drinking water reduces the incidence of dental caries in children and adults by 20 to 40%, and drinking water fluoridation has proven to be the most effective and inexpensive method of controlling and preventing dental caries. The beneficial effects of fluoride consist in the replacement of hydroxyl ions in the apatite crystal lattice of enamel and dentin. In this way, the apatite crystals become less soluble for the bacterial acids and, accordingly, the development of caries is slowed down. Remineralization of hard dental tissues is also carried out. If the beneficial cumulative daily dose for children up to 6 years of age of 0.8-1 mg is exceeded, the adverse effects of fluoride can be manifested – if the concentration is increased systemically, chronic fluoride intoxication and dental fluorosis appear, which is manifested by a change in enamel structure (becomes more brittle), whitish or darker discolorations and spots appear. Fluoride can directly damage ameloblasts or interact with various enzymes during the synthesis, maturation and mineralization of the enamel matrix. Therefore, when an insufficient presence of fluorine in the drinking water and a risk of developing dental caries is detected, for children under 6 years of age, the dentist may prescribe additional intake, but it must be well calculated, since fluoride is also taken from other places – green tea, various foods, especially seafood, some fruits, etc. Fluor-

ride supplements can be prescribed for children between the ages of 6 months and 16 years, depending on the dose of fluoride in drinking water, age, risk of caries development, intake of fluoride from other sources. (46-51)

Once past the stage of enamel formation, the risk of developing dental fluorosis decreases significantly. (51)

Fluorine prophylaxis can be carried out exogenously and endogenously. In the exogenous (local) way, professional, individual and community-based methods are used. Professional prophylaxis is carried out in the dental office by the dentist with fluoride solutions, varnishes, gels, foam, systems for slow release of fluoride and others with different fluoride content. Individual prevention includes the individual's personal use of fluoridated toothpastes, solutions, gels, dental floss, chewing gum, candies, etc. The concentration of fluoride in these sources is lower compared to those for professional use. Community-based prevention is carried out in collectives by means of fluoride solutions, toothpastes, etc., but compared to professional and individual prevention, it is not so recommended. Endogenous prevention is community-based, group and individual. The first is carried out with fluoridation of water and salt. Group prophylaxis includes the prescription of fluoride tablets, fluoridated milk, mineral water with fluoride, and individual prevention is carried out by the individual using fluoride tablets, drops, mineral water with fluoride, etc. (46-51) For children up to 3 years of age, immediately after the appearance of the first tooth in the mouth, a toothbrush and an amount of fluoridated toothpaste equal to a grain of rice is used. For children between 3 and 6 years of age – the amount of fluoridated toothpaste should not be larger than a pea. The teeth are brushed 2 times a day, taking special care not to swallow the toothpaste. That is why the amount of fluoride in children's toothpastes is significantly lower compared to adult toothpastes – 400-500 ppm compared to 1400-1500 ppm for adults. Fluoride solutions are used by children at least 6 years old – to minimize the effect of a possible overdose and to be sure that the child realizes that he should not swallow the paste and may spit. Scientific studies in Europe have proven that even the use of toothpastes with 1000 ppm fluoride by children under the age of 6 would not create a danger of developing dental fluorosis. However, the amount of fluoride ingested from all sources should be monitored. (46, 49)

Ingestion of large amounts of toothpaste with a high fluoride content leads to acute systemic toxicity that begins with signs from the gastrointestinal tract, neurotoxic effects and effects on memory and learning are observed. The toxic dose (or, more precisely, the minimum dose that would cause the need for emergency medical measures and hospitalization due to life-threatening conditions) of fluoride is 5-8 mg/kg body weight. (48-50)

Sodium lauryl sulfate is the most commonly used anionic detergent to improve the washing action of toothpastes. It has been shown that the substance can dehydrate, cause inflammation, desquamation of the oral epithelium and increased occurrence of oral lesions. The compound is thought to denature the mucin layer on the oral epithelium, thereby exposing the underlying epithelium – increasing the possibility of developing aphthous lesions. Therefore, patients who suffer from xerostomia or have sensitive mucous membranes are advised to avoid products that contain the mentioned compound. It is believed that lauryl sulfate also increases the permeability of the mucous membrane to metal ions and other sensitizing substances, and also – reduces the effectiveness of fluoride compounds in the fight against caries. (52-53)

Triclosan is a broad-spectrum antibacterial agent that is used in toothpastes and mouthwashes to enhance their anti-plaque and anti-inflammatory effects. In scientific studies of monolayer cell epithelial cultures, it has been shown that it can induce apoptosis processes in human gingival fibroblasts. In human and animal studies, on the other hand, triclosan has been found to reduce the inflammatory potential of sodium lauryl sulfate. Although the allergenic potential of triclosan is considered low, reports of allergic reactions are available. Scientific studies have found that triclosan can combine with chlorine from drinking water to form chlorinated organic compounds and chloroform, known carcinogens. (38-42)

Various types of rinsing solutions (mouthwashes) are known in the art. Those with the addition of 0.05% sodium fluoride are recommended for daily use in the fight against caries. Anti-plaque mouthwashes contain antiseptics such as chlorhexidine, essential oils, cetylpyridine chloride, triclosan. Due to the side effects of long-term use, anti-plaque mouthwashes are recommended for short periods of use. Desensitizing (to reduce sensitivity) mouthwashes are created with the addition of potassium



nitrate and arginine. (38-39)

Chlorhexidine is a widely used cationic bisguanidine antiseptic with broad-spectrum antibacterial action, known in three forms: digluconate, hydrochloride and acetate. Can be found as rinse water (0.2%), gel (1%), spray (0.2%), toothpaste (1%), endodontic treatment irrigant (2%), varnish and periodontal chips as a topical antimicrobial placed in periodontal pockets. The use of chlorhexidine rinses is recommended for short-term use in patients with fixed jaws due to trauma, with blood disorders, after chemotherapy, radiotherapy, bone marrow transplants, when placing orthodontic appliances and braces, as adjunctive therapy after periodontal treatment and to combat with halitosis. There are a number of scientific studies that confirm the good biological effects of chlorhexidine. As a cationic substance, it binds to the surface of the enamel through the anionic (negatively charged) components – free carboxyl, sulfate, phosphate groups, and also with salivary glycoproteins. In this way, the formation of the pellicle is reduced, as the adhesion of the proteins that form it is slowed down – the formation of plaque is prevented. Chlorhexidine also permanently binds to the surface of bacteria, inhibiting their colonization on tooth surfaces. The effect is also beneficial on existing gingival and periodontal inflammations. (54-56)

Side effects of chlorhexidine after long-term use (more than 2 weeks and in high concentrations) are brownish staining of the teeth, mucosa, existing obturation, disturbances in taste perception, erosions of the oral mucosa, swelling of the parotid (surrounding the ear) salivary glands, increased formation of supragingival calculus. Rare anaphylactic cases have also been reported following the use of chlorhexidine mouthwashes or gels. Use in pregnant women must be justified – it is classified in class B according to its teratogenic activity. For this reason, despite its extremely good biological effect, its use must be very careful. (54-59)

Cetylpyridine chloride in the composition of some washing solutions is a cationic ammonium agent with antibacterial and antiplaque properties. Scientific studies have shown it to be a suitable adjunct in plaque reduction and gingival inflammation therapies. It combines very well with chlorhexidine and is placed in similar combinations – it neutralizes toxins that are released after the death of gram (-) bacteria. Undesirable effects include tooth discoloration, taste changes, and burning sensations. (60, 61)

Essential oils have been used for many years to fight plaque and gingivitis. Scientific studies have shown that their effectiveness in fighting plaque and gingival inflammation is even similar to that of chlorhexidine preparations. Thymol, menthol, eucalyptol oils, methyl salicylate and other compounds are used in various concentrations. The most common side effect of these substances is altered taste. Rare reversible allergic reactions such as rash on the palate have also been reported. In general, no other negative effects or mucosal changes are mentioned in the literature, however, patients suffering from xerostomia should be especially careful. The absence of genotoxic effects of rinses containing essential oils, chlorhexidine, triclosan after 2 weeks of use was also demonstrated by cytogenetic studies on three-dimensional models of human oral tissues and double-blind, randomized clinical trials on patients. (62)

Alcohol is a well-known carcinogen. There are both scientific studies that do not establish a link between ethanol-containing mouthwashes and an increased risk of developing oral carcinomas, and those that do. The American Dental Association issued a statement in 2009 that alcohol-containing rinses are a good anti-plaque and anti-inflammatory control when used as recommended. However, some individuals are at greater risk of developing oral cancer due to lifestyle or genetic predispositions. Therefore, individuals who smoke, have a certain intolerance to alcohol, have risk factors for developing oral cancer, have had it in the past, or suffer from another cancer should reduce or even eliminate the use of rinses containing alcohol.

Benzylamine hydrochloride, a well-known anti-inflammatory agent from medicinal products to combat sore throats, is used in rinsing waters to reduce discomfort and inflammation of the oral mucosa in various disorders of its integrity, after oral surgery, etc. Studies have proven that the substance has antimicrobial qualities and can be combined with other therapeutic preparations. Although a known genotoxic effect of benzylamine hydrochloride has been demonstrated in some animal species in a scientific study, the only potential adverse effects in humans are mucosal paresthesia and photoallergic contact dermatitis of the lips and chin. (64)

Sodium bicarbonate has no antibacterial effects, but has a good washing effect. Increases the pH of oral agents and prevents the development of acidophilic bacteria. According to a scientific study, it causes

less irritation of the oral mucosa. The substance is cheap, easy to find and prepare a washing solution. (59)

Rinses containing povidone-iodine or betadine (1%) are used as a relatively effective antibacterial agent in the treatment of acute oral mucosal infections, in combination with periodontal treatment and after oral surgical interventions to reduce the bacterial load in the oral cavity. Side effects should be mentioned, however, such as mucosal irritation and hypersensitivity, type 1 allergic reactions, effects on the thyroid gland after long-term use, renal function disorders. With the emergence and development of the global pandemic in 2020 from the SARS-COV-19 coronavirus, scientists are studying the virucidal potential of povidone-iodine solutions, and at the moment the results are more than encouraging – in one of the studies, in 30 seconds of contact with the oral mucosa of a 1% povidone-iodine solution, the virucidal activity is more greater than 99.99%. However, more scientific studies are needed to confirm this effect. (64, 65)

Hydrogen peroxide, also known as oxygen water, is an oxidizing agent used in some mouthwashes (1.5%) recommended to kill anaerobic bacterial flora. It also has a mechanical washing effect, due to the oxygen released into bubbles when in contact with organic tissue or food residues. Genotoxicity in vivo has not been proven, as the body contains enzymes that degrade the substance. Animal studies have found dose-dependent tumorigenic effects of the gastrointestinal tract. The agent is relatively safe for use in humans, in the permitted concentrations. (66-68)

However, higher concentrations of hydrogen peroxide are used in teeth whitening products. An active ingredient in a number of whitening gels and strips is carbamide peroxide, which releases hydrogen peroxide when it reacts with water. According to the European cosmetic regulations of 2012 adults

and children are prohibited from using products that release more than 6% hydrogen peroxide. This is equivalent to 18% carbamide peroxide. According to scientific studies, 10% carbamide peroxide used for whitening for 5 weeks can cause the cells in the gums (gingival mucosal epithelial cells) to grow. The most common side effects after whitening are tooth hypersensitivity, which is greater after activating the peroxide gels with light or heat. Moreover, the effectiveness of light activation of a gel with a high peroxide content has not been statistically proven. As for peroxide bleaching strips, those in which the concentration is up to 6% can be safely used for up to 2 weeks for external whitening. (66-70)

Dental adhesives for retaining complete dentures are divided into soluble adhesives (various gels, powders, creams) and insoluble ones (tapes and pads). Various polymers, carboxymethylcellulose, zinc and calcium salts are used in their composition. According to a number of scientific studies, they significantly improve the retention and function of removable prosthetic structures when, despite compliance with all the rules for their manufacture, their use is required. There is not enough evidence in the literature about their influence on the human organism. Bacterial and fungal contamination of adhesives, possible cytotoxicity, neurological problems in conditions of increased intake of zinc-containing agents have been reported. (71-72)

Conclusions

Medical and dental specialists should pay special attention to the content of the materials they implement in their treatment plans on a daily basis. Being profoundly informed on the general diseases, medications usage and allergic status of their patients can prevent adverse complications. Although medicine explores and studies in depth possible biological reactions, still they may occur.

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