THE INNOCUITY OF TRICLOSAN. A REVIEW

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REZUMAT
Triclosanul este unul din agenţii antimicrobienci ai cavităţii bucale cei mai cercetaţi astăzi. O conferinţă de consens desfăşurată la Hilton Athenee Palace București în 15 februarie 2008, organizată de Colgate-Palmolive România, a reunit concluziile unor lideri de opinie în sănătate orală din România cu privire la aplicabilitatea triclosanului şi tehnologia triclosan-copolimer PVM/MA în medicina dentară. Articolul redă datele prezentate în cadrul conferinţei de consens privind valoarea triclosanului în produsele de igienă şi terapeutice utilizate în medicina dentară. Cu referire la siguranţa utilizării agenţilor antimicrobieni în medicină şi la efectul triclosanului în managementul afecţiunilor oro-dentare, concluzia desprinsă din literatura de specialitate pusă la dispoziţie este că utilizarea pastei de dinţi ce conţine asocierea triclosan-copolimer PVM/MA are un pronunţat efect antibacterian, iar interacţiunea triclosanului cu celulele bacteriene - inocuitatea celulară a triclosanului - nu prezintă efecte negative asupra flori bactereiene cu posibilitatea apariţiei unor tulpini mutante.

Cuvinte cheie: triclosan, bactericid, bacteriostatic, enzime, membrana celulară, dezinfecţante, antibiotice

ABSTRACT
Triclosan is currently one of the most researched antimicrobial agents of the oral cavity. A consensus meeting organized by Colgate-Palmolive Romania took place on February 15, 2008 at Athenee Palace Hilton Bucharest to collect the conclusions of Romanian opinion leaders regarding the applicability of triclosan in dental medicine, and the triclosan-PVM/MA copolymer technology. The article reflects the data issued by the consensus meeting regarding the value of triclosan as therapeutic agent of the periodontal disease. With respect to the safety of the use of the triclosan–PVM/MA copolymer in the management of oro-dental diseases, the conclusion of the literature is that a toothpaste containing the triclosan – PVM/MA copolymer combination offers a pronounced antibacterial effect and its interaction with bacterial cells – the innocuity of Triclosan – does not determine any negative reactions such as the development of mutant bacterial subspecies.

Key words: triclosan, bactericidal, bacteriostatic, enzymes, cell membrane, disinfectants, antibiotics.

INTRODUCTION
The use of triclosan in preventive dentistry has become well known because of its antibacterial qualities as well as the reduced number of secondary effects reported along its utilization in time.

Microorganisms in the oral cavity are the basis for bacterial plaque formation. Microbial cultures develop in a warm, dark and highly acid environment. These conditions are reached inside the oral cavity several times a day, and especially during the night. Bacterial plaque is a dense and coherent mass of microorganisms in an intermicrobial matrix rich in polysaccharides and glycoproteins, which adheres to the surface of hard and soft oral tissues and to the surface of odonto-prosthetic reconstructions by means of the acquired layer. It remains adherent despite bacterial colonization on dental surfaces, vigorous rinsing or irrigations. To fight against bacterial colonization of dental surfaces, various dental hygiene materials, such as mouthwashes and toothpastes containing different antibacterial agents with potential harmful effects on the microorganisms involved in the initialization and progress of the lesions, have been created.

One of the antibacterial agents frequently used in dental hygiene products is triclosan. Triclosan has a long and beneficial history. Ciba invented this product 35 years ago and it has been applied ever since without any adverse effects. Triclosan is the first choice antibacterial active ingredient in

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dentifrices, anti-acne formulations and is valuable in many medical applications. It persists on the skin or on other surfaces after washing, thus providing a long term action against germs. Triclosan is safe and effective: it slows down or stops bacterial growth. It is used in products such as soaps, deodorants and toothpastes, helps preventing bacterial dissemination, reduces the infection risk, controls the body sweating and may prevent dental diseases.

Triclosan has important antibacterial properties, but it also may sometimes be used for its antifungal and antiviral properties.

It may be found on the market under various names: Microban – when included in plastics and cloths; Biofresh – when included in acrylic fibers. The popularity of the substance is given by its unique properties regarding the effectiveness against an impressive number of bacteria. A large database of clinical trials certified its use for more than 35 years with no major side effects, confirming the fact that triclosan is effective and equally safe for humans and for the environment.

Once penetrated into the cell, triclosan inhibits the enzyme enoil-acyl protein reductase (FabI), preventing bacteria from producing the fatty acids required for cell membrane formation and for other vital functions. Humans are not equipped with the enzyme, so that triclosan remains harmless for humans. One triclosan molecule permanently inhibits one FabI molecule, which explains why triclosan has a strong antibacterial action even at very low concentrations. Triclosan especially acts on the permeability of the cytoplasmatic membrane and on intracellular targets, inhibiting FabI.

Triclosan, by its action and effects, belongs to the biocides category, a group of chemicals with antiseptic and disinfectant effects. Triclosan has bacteriostatic effect at low concentrations and bactericide effect at high concentrations. As a result of its bacteriostatic activity against a wide range of Gram negative and Gram positive bacteria, it has become a popular component of personal use products such as deodorants, antiperspirants, wash gels, cosmetics, antimicrobial ointments, lotions, solid and liquid soaps. It is also used as an additive in plastics, polymers and textiles in order to render them antibacterial properties. As for oral hygiene materials, the substance has proven its qualities in toothpastes and mouth washes, being a beneficial ingredient, effective against microorganisms involved in bacterial plaque formation.

The results of studies performed and published in prominent, peer reviewed journals revealed the fact that, throughout researches, no opportunistic pathogens or triclosan-resistant strains have been detected in the oral microbial flora.\(^1\)

The triclosan-containing toothpastes and the innocuity of triclosan

Nowadays, toothpastes target the same principles as hundreds of years ago, the difference residing in the fact that modern products are more sophisticated in composition and include dedicated components, which highly recommend them both therapeutically and esthetically. Patients these days expect toothpaste to remove bacterial plaque, to leave the teeth shining, to maintain and improve periodontal health, to decrease the incidence of caries and to provide a fresh breath.

Adding triclosan molecules in toothpastes renders these products special qualities. In order to increase these benefits, the improvement of triclosan effectiveness by developing a system which increases the sedimentation period of dental plaque becomes necessary. A co-polymer of polyvinyl-methyl ether (PVM) and maleic acid (MA), proved to be adequate for this purpose, retaining triclosan on the hard and soft oral surfaces for several hours.

As mentioned above, the molecular specificity of triclosan resides in its capacity of interacting with the enoyl-acyl carrier protein reductase (FabI). This enzyme is essential for the synthesis of bacterial fatty acids in numerous bacterial species, including Gram positive ones. This target is common with that of an antibiotic used against tuberculosis, the isoniazid. Bacterial response to triclosan is at the same time specific, because it is centered on a single enzyme, and also non-specific, because it involves a high number of disturbances of bacterial structural elements, such as the cell membrane. Action mechanisms initially involve the active penetration of the biocid or antibiotic in the Gram-negative bacteria (the effect is augmented by permeabilization agents), and the passive diffusion in Gram-positive bacteria, the mechanism being accompanied by membrane alterations. Once entered the bacterial cell, the biocid induces stress conditions and stimulates the expression of thermal shock, which represents a response to aggression. The oxidative stress has a significant role in the cellular peroxidant/antioxidant ratio. Bacteria try to survive, but under inhibiting or inactivating the metabolic conditions in a cellular tolerance/resistance context, the bacterial cell, in response, releases ionic effluxes. The efflux is a mechanism known to interfere with the bacterial resistance to antibiotics, biocides and other antibacterial substances. The efflux results from the presence of membrane and cytoplasmatic proteins. Efflux pumps may be stopped by blocking devices.
Triclosan determines the overexpression of efflux pumps, both on laboratory-grown cell colonies and on cultured cells obtained from clinical samples.

In the context of triclosan innocuity, the antiinflammatory activity of this biocid must be underlined. The production of interleukine 1β, an inflammation mediator produced by gingival fibroblasts stimulated by tissue necrosis factor α (TNF-α), is reduced by triclosan. The histamine-induced inflammation is also decreased by triclosan.

There is a probability that chronic use of triclosan facilitates the selective development of bacteria, which may result in a decreased susceptibility to this biocid. Intrinsic resistance (non-susceptibility) of bacteria to antibacterial substances is primarily due to the impermeability of the membrane barrier. This is especially true for mycobacterial spores, Gram-negative bacteria, and vancomycin-resistant strains of Streptococcus aureus. Enterococci are less susceptible than staphylococci. Non-susceptibility to triclosan may occur following mutation, adaptation or artificial insertion of plasmids or other genetic elements, but despite all these it is unlikely to actually occur. These phenomena take usually place when bacterial strains are exposed to increasing antibiotic or biocide concentrations, which does not occur in natural conditions.

According to the literature, resistance mechanisms to triclosan involves:

- intrinsic factors of non-susceptibility, which may be either due to a reduction in biocid penetration (alteration of efflux processes), or to inactivation by a major triclosan resistance mechanism,
- acquired factors aiming the alteration of targets, their inactivation or modification, the efflux, the shift from a sensitivity stage, hyperproduction of a target, lack of the metabolic pathway of an enzyme etc.

In theory, triclosan-induced selection of certain bacterial strains may lead to the occurrence of resistant strains. Mutations of enoyl-reductase have been identified as well as the overexpression of efflux pumps. There are still questions on the possibility of a horizontal transfer of FabI mutations to environmental bacteria and to non-nosocomial pathogens. Despite all that, ACP isoenzymes, which constitute a functional equivalent of FabI, have a different sensibility to triclosan, which removes this risk.

Part of these mechanisms may produce cross-resistance between biocides and other antibacterial substances, including antibiotics. Most antibiotics have a specific target (DNA, RNA, protein synthesis), whereas biocides have multiple targets. Their action depends on their concentration, the effects being discrete at low concentrations and highly manifest at high concentrations. Antibiotics and biocides may share common mechanisms. Nevertheless, these changes in the susceptibility of known bacterial species (both clinically and in vitro) for antibiotics do not seem to materialize in the case of biocides. Some authors think that these are inevitable and menacing facts but, for the moment, they are not able to fundament these assertions. The main problem does not refer to the evolution of triclosan-resistant strains but to the risk of selecting and favoring strains which could also be resistant to antibiotics. For now, this risk has not been scientifically proven.

The use of triclosan in hospital environment and in clinical cases contributes to the limitation of pre- and post-surgical infections. As a consequence, this allows the reduction of antibiotic use, the effectiveness of which has significantly decreased during recent years for increasing dosages.

**CONCLUSIONS**

Triclosan-induced bacterial strain selection may in theory lead to the occurrence of resistant strains, which may result in public health problems, as they are prone to become resistant to antibiotics.

Mutations of enoyl-reductase have been identified as well as the overexpression of efflux pumps. There are still questions on the possibility of a horizontal transfer of FabI mutations to environmental bacteria and to non-nosocomial pathogens. Despite all that, ACP isoenzymes, which constitute a functional equivalent of FabI, have a different sensibility to triclosan, which removes this risk.

The main question does not refer to the evolution of triclosan-resistant strains but to the risk of selecting and favoring antibiotic resistant strains as well. For the moment, this question has remained unfounded.

The use of triclosan contributes to the limitation of pre- and post-surgical infections. This allows the reduction of antibiotic use, the effectiveness of which has significantly decreased for increasing dosages.

Literature data support the continuation of triclosan use, provided „we remain within the space of reason, rather than emotion”.

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REFERENCES