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Polyhexanide (PHMB) – properties and applications in medicine

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ABSTRACT: Polyhexamethylene biguanide (PHMB) is one of the many antiseptics available in the medicine. It stands out from the others with its numerous advantages. It has a low toxicity factor, chemical stability, and bactericidal effect on most microorganisms. PHMB is used in many areas of medicine, veterinary medicine, gastronomy, and industry. The application of polyhexanide in the treatment of chronic wounds allows for fast regeneration and reduced time of wound treatment and hospitalization. According to the Recommendations of the Polish Wound Treatment Society, PHMB is recommended in treatment of critically colonized wounds, wounds at risk infection, burns, and decontamination of acute and chronic wounds, and as second choice in infected wounds.

Keywords: Polyhexanide; PHMB; Polyhexamethylene biguanide; Antiseptic; Antimicrobial; Wound.

1. INTRODUCTION

Chronic wounds are very important medical problem. It is estimated that about 1-1.5% of the population suffers from chronic wounds. Simultaneously, this illness affected approx. 3% of the population above 60 years of age [1, 2]. It is supposed that in Poland there are almost 500,000 of such patients [2]. In Poland, according to the guidelines, the following antiseptics are used to treat wounds: octenidine dihydrochloride, polyhexanide, PVP-iodine and products based on hypochlorite [2, 3]. This article provides information on polyhexanide (PHMB).

2. CHEMICAL ASPECTS

Poly(hexamethylene)biguanide hydrochloride (PHMB) is one of the most effective surface-disinfectant and anti-infective agent. It is a biocide from the bisbiguanid family and characterized by excellent anti-microbial activity. Moreover PHMB (Figure 1) is chemically stable and has a low toxicity index [4].

Research on PHMB from the 20th century has shown that poly-biguanides are strongly antibacterial, compared to molar particles carrying only one group of biguanide. In polyhexane the number of biguanide

residue is n = 2-40, and an optimal number of methylene groups in the walk between the biguanide residues is m = 6. The terminal groups of this chemical compound are amine and cyanoguanidine [5].

Most commonly used method for polyhexanidine synthesis is polycondensation of sodium dicyandiamide and hexamethylenediamine in two stages [4].

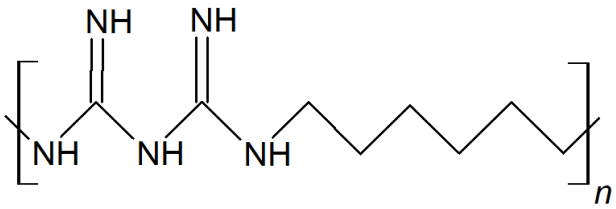

Figure 1. Chemical structure of PHMB.

3. TOXICITY ASPECTS

According to the Commission Regulations (EU) No. 944/2013 and 2019/831, the PHMB is classified as CMR 2 (Carcinogen of category 2). CMR substances are substances that are classified as carcinogenic, mutagenic, or toxic for reproduction in cosmetic products [6, 7]. In the opinion of the Scientific Committee on Consumer Safety the use of PHMB as a preservative in all cosmetic products is safe up to 0.1% [8].

Polyhexamethylene biguanide hydrochloride (PHMB HCl) was classified as a hepatic tumorigen in mice. In the studies was used the highest dose (30 mg of 10% PHMB HCl in ethanol), applied to the skin daily (5 days/week) for 80 weeks. An increase in the incidence of liver tumors was observed and statistically significant was only for liver tumors of endothelial origin. In this group was observed high mortality (76 to 78% of animals died) [8, 9]. PHMB was also evaluated for use in product-type 1 (human hygiene), product-type 5 (drinking water), and product-type 6 (preservatives for products during storage), and product-type 9 (fibre, leather, rubber and polymerised materials preservatives), as defined in Annex V to Regulation (EU) No 528/2012. PHMB is not approved as an active substance for use in biocidal products of product-types 1, 5, 6, and 9, since the risk identified in the human health and environmental assessments was regarded as unacceptable [10, 11].

Among side effects, PHMB can lead to dermal and ocular irritation, dermal and oral toxicity [8]. Moreover, two cases of a possible anaphylactic reaction triggered by PHMB were described [12]. One patient with a grade III anaphylactic reaction had IgE against both PHMB and chlorhexidine [13].

The use of PHMG as a component of aerosol disinfectants and air humidifiers is widespread. However, a causal link has been proven between the use of such disinfectants and the development of diffuse pulmonary fibrosis and other idiopathic fibrous interstitial pneumonias. Mice that received intravenous guanidine PHMG (1 mg/kg = 0.001 ug/mg) showed pulmonary oedema, inflammatory cell leakage, increased lung water accumulation and decreased collagen content [14]. The most known and important contraindications for PHMB are: the above mentioned possible allergy and the application during the first 4 months of pregnancy (in later stages of pregnancy its use should follow strict observance of a benefit-risk assessment). Naturally, the peritoneal lavage with PHMB in septic peritonitis is also contradicted [15].

4. MADE OF ACTION

Scientists established that the killer effect of PHMB is to affect the cytoplasmic membrane of microorganisms and damage it immediately. They act through a dual mechanism of membrane integrity

disruption and selective condensation and chromosome damage. After being combined with negatively charged phosphate groups of phospholipids present on the bacterial cell membrane, leads to its stiffening and tearing. It subsequently leads to the death of the bacterial cell [4]. Diffusion and irreversible loss of potassium from the intracellular pool of K+ ions occurs [16]. Another unique feature recently identified for polyhexanide is its intracellular bactericidal activity, considered an important property in the potential treatment of skin infections caused by intracellular bacteria [17].

The results of research carried out on human osteoblasts (hFOB) and endothelial cells raise doubts about the positive results of the use of PHMB in bone cement in the management of total arthroplast infections. The data showed that even at very low concentrations polyhexanide has a negative effect on bone cell viability and number [18].

5. APPLICATION

Polyhexanide-containing agents have been used in various areas, mainly for disinfection of solid surfaces in hospitals and veterinary clinics at 0.1-0.2% concentration. PHMB is applied in rinses, thanks to its effectiveness in inhibiting biofilm regrowth. The research has shown that oral rinses containing 0.04% and 0.12% PHMB inhibit the growth of dental plaque and reduce the number of bacteria in the oral cavity much more effectively than placebo and triclosan, but much less than chlorhexidine [19].

Polyhexanide is increasingly used as an active ingredient in a number of products, such as wet wipes, wound winding solutions, sterile dressings and disinfectants, as well as in personal and pharmaceutical hygiene products to treat chronic wounds and burns [20]. Products containing polyhexanide are becoming increasingly important in the treatment of wounds worldwide. They are eagerly used by patients with pain-sensitive wounds, without significantly changing their quality of life, but with a positive impact on their well-being [21].

Polyhexanide is currently considered one of the most suitable antiseptics for chronic wounds, epithelial and endothelial lesions, including second degree burns. Apart from its antiseptic efficacy, it does not inhibit the reepithelialization process [22]. It also prevents secondary bacterial infection. All these advantages have contributed to a reduction in the number of dressings and thus in treatment costs [23]. A purified collagen matrix containing polyhexamethylene biguanide with antibacterial properties was developed to support wound healing. The dressing consists of two layers of type I collagen matrix and has the ability to quench proteolytic enzymes [24].

Polyhexanide-based antiseptics are an alternative procedure for the care of healthy exit sites and an effective and safe therapy to prevent exit site infection (ESI) and peritonitis, which are common peritoneal dialysis (PD) complications [25]. Agents containing 0.02% polyhexanide can be effectively used for perioperative antiseptic eye prophylaxis [26] and in antibacterial fluids for optical lens containers in order to prevent the formation of biofilm by myco-organisms [27]. In dentistry, PHMB in concentrations of 0.05-0.2% is added to root canal sealants (to zinc eugenol cement), thanks to its antibacterial properties. It is aimed at maintaining a sterile environment of the prepared root canals [28].

In Poland are used antiseptics containing PHMB + Ringer solution, PHMB + betaine and PHMB + poloxamer. According to the Recommendations of the Polish Wound Treatment Society, PHMB is recommended in treatment of critically colonized wounds, wounds at risk infection, burns, and decontamination of acute and chronic wounds, and as second choice in infected wounds [2].

6. ANTIMICROBIAL ACTIVITY

Polyhexanide is effective against yeasts, viruses, Gram-positive and Gram-negative bacteria and some parasites. The significance of PHMB as an antiseptic substance in the treatment of infected wounds and in decolonization of skin with bacteria in biofilms has increased. Many *in vitro* studies evaluated the effectiveness of antiseptics, including PVP-iodine, octenidine dihydrochloride (OCT), polyhexanide (PHMB), hydrogen peroxide, chlorhexidine digluconate (CHX) or ethacridine lactate in infections caused by *Staphylococcus* strains, *Pseudomonas aeruginosa*, *Enterococcus faecalis* and *Klebsiella pneumoniae*. Studies showed that octenidine and polyhexanidine were the most effective in relation to the tested strains in both planktonic and biofilm culture [29-32]. Unfortunately, PHMB in many trials was shown to need more time in comparison to octenidine to reach the desired level of efficacy (PHMB: 15-30 min.; OCT: 30 s to 1 min.) [33]. PHMB has anti-biofilm activity, therefore, it can be an interesting option in the treatment of biofilms on artificial surfaces [34].

In comparsion of activity of 0.2% PHMB, 2.5% sodium hypochlorite and 0.2% chlorhexidine against *Enterococcus faecalis*, *Staphylococcus epidermidis* and *Candida albicans* was shown that PHMB and NaOCl showed almost the same effectiveness, while CHX was less effective, especially for *E. faecalis* [35]. Polyhexanide has a bactericidal effect also on methicillin-resistant *Staphylococcus aureus*. The research showed that PHMB is a active with a minimum MIC of 1 µg/mL [29].

Prolonged *in vitro* exposure to low levels of polyhexanides may cause reduced sensitivity of MRSA strains to polyhexanide without coexisting cross-resistance to chlorhexidine. However, reduced susceptibility of polyhexanides may be accompanied by changes in susceptibility to other antibiotics such as vancomycin, teicoplanin and daptomycin. Moreover, it were identified mprF mutations in all MRSA strains showing resistance to polyhexanide [17].

In vitro studies conducted on *Leishmania* sp. confirmed the killing activity of polyhexanide on promastigots at sub-micromol levels in a dose-dependent manner. The antiseptic proved to be more potent than current standard anti-inflammatory drugs used in clinics. In addition, it directly kills parasites through a dual mechanism involving both penetration of parasitic membranes and selective condensation and disruption of parasitic chromosomes [36]. Furthermore, other *in vitro* study has proven the efficacy of 0.02% PHMB against *Acanthamoeba* cyst in patients with positive *Acanthamoeba* keratosis [37].

Polyhexanide also exhibits time- and concentration-dependent antifungal activity. The research revealed that polyhexanide had the strongest flow against isolates of *Fusarium* and *Exophiala*, but showed minimal activity against isolates of *Aspergillus flavus* and *A. terreus*. It is therefore used as an antiseptic in contact lens solutions to prevent the development of fungi leading to eye infection [38].

7. CONCLUSION

The increase in resistance of bacteria to antibiotics complicates the treatment of infections. Antiseptics provide low bacterial tolerance and have a broad spectrum of antibacterial effect. PHMB is a substance with good antimicrobial activity and safety.

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Conflict of Interest: The authors declare no conflict of interest.

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