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Review Article

Octenidine Dihydrochloride: A New Age Antimicrobial Agent

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Abstract

Chlorhexidine, that is an example of second generation chemical plaque control agent, possess cationic properties. For the past 40 years, it has been rigorously investigated and found that it possess superior antiplaque activity as compared to any other antimicrobial agents and hence, it is considered as a gold standard for plaque control. However, its long term use is prohibited because of certain side effects. The most common side effect associated with its long term use is the extrinsic staining. Some evidence in the literature also suggests that its frequent use lead to the alterations in the taste sensations, desquamation of the oral mucosa etc. These drawbacks led to the development and usage of other plaque control agents such as Octenidine dihydrochloride. Octenidine dihydrochloride, is an antimicrobial cationic surfactant and it belongs to the second generation of chemical plaque control agents. It was developed at the Sterling-Winthrop Research Institute, Rensselaer, NY in the 1980s. A concentration of 0.1% in mouthwashes along with different additives, flavouring agents and excipients is approved for the treatment of gingivitis, halitosis, as pre and post-surgical periodontal and oral procedures.

Keywords: Octenidine Dihydrochloride; Chlorhexidine; Mouthwashes; Second Generation Chemical Plaque Control; Periodontal Disease

Abbreviations

OCT: Octenidine Dihydrochloride; CAS number: Chemical Abstracts Service Registry Number; CHX: Chlorhexidine; MRSA: Methicillin-Resistant Staphylococcus Aureus; MIC: Minimum Inhibitory Concentration; PVP-I: Povidone Iodine

Introduction

Periodontal disease is a common disease that is mostly neglected by the general population. Despite of the presence of numerous mechanical plaque control methods, these methods are still not sufficient for complete removal of plaque mainly in the inaccessible areas inside the oral cavity. Hence, chemical plaque control methods are advised mainly to the patients who are likely to develop periodontitis. Chemical plaque control methods are mainly used in the form of mouthwashes and unlike a toothbrush a mouthwash can easily decrease microbial load, as it effectively rinses the oral cavity including the inaccessible areas, hard as well as soft surfaces of the oral cavity. Antimicrobial mouthwashes serve as a useful method of oral hygiene in older age patients, patients who cannot brush their teeth on their own due to illness or mentally and physically challenged patients. Mouthwashes available in the market are usually a combination of astringents, antiseptics, essential oils, breath fresheners, flavouring agents etc [1]. There are mainly two types of mouthwashes available in market, chemical and herbal. The chemical plaque control agents are divided into first generation such as quaternary ammonium compounds, phenols, second generation such as bisbiguanides- chlorhexidine gluconate, and third generation such as delmopinol [2].

Chlorhexidine, that is an example of second generation possess cationic properties. It was evolved in the late 1940s during the search for the antiviral agents. But it was found that, it possesses antibacterial action rather than antiviral activity and hence, its use started as a general disinfectant. It was first used in the dental practice as a root canal disinfectant and for cleaning the operation sites and later on for the prevention of the caries, denture disinfection, dry socket treatment, plaque control, apthous ulcers etc. For the past 40 years it has been rigorously investigated and found that it possess superior antiplaque activity as compared to any other antimicrobial agents and hence, it is considered as a gold standard for plaque control. This is due to the fact that other antimicrobial agents lack the substantivity and the efficacy against the microorganisms [3]. Its long term use is prohibited because of certain side effects. The most common side effect associated with its long term use is the extrinsic staining. Some evidence in the literature also suggests that its frequent use leads to the alterations in the taste

sensations, desquamation of the oral mucosa etc [4]. These drawbacks led to the development and usage of other plaque control agents such as Octenidine dihydrochloride. Octenidine dihydrochloride, is an antimicrobial cationic surfactant and it belongs to the second generation of chemical plaque control agents. It was developed at the Sterling-Winthrop Research Institute, Rensselaer, NY in the 1980s. A concentration of 0.1% in mouthwashes along with different additives, flavouring agents and excipients is approved for the treatment of gingivitis, halitosis, before surgical periodontal procedures etc. Hence, this article provides an overview of Octendine dihydrochloride and its uses in dental as well as other fields.

Chemical properties

Octenidine dihydrochloride is a cationic surfactant that has the ability to decrease the surface tension of water and is non-volatile. The lowered surface tension of water is due to the existence of hydrophobic and hydrophilic end present in molecule. The stability of Octenidine is in between the pH range of 1.6- 12.2. Two cationic centres are present in the molecule of OCT, which do not interact with one-another [5]. OCT is less reactive with free chlorine and hence can be used along with sodium hypochlorite for irrigation [6]. As Povidone Iodine let outs iodine radicals, it can react with Octenidine that can lead to irritation of the tissues and brown-to-violet discoloration [7]. It can also precipitate in presence of the preservatives like parabens, sorbic acid and benzoic acid that are commonly used in cremes [8]. Its properties does not get altered under light and its storage can be done at room temperature. Its sterilization can be done at 130 C with steam [9]. It consists of two centres that are cationically active, hence allowing the Octenidine to bind with the surfaces that are negatively charged such as envelopes of microbial cells and eukaryotic cell membranes. On application to the mucous membrane, wounds or skin, it gets activated against enveloped viruses, bacteria and fungi as it has the affinity for the phospholipids and polysaccharides. It is microbicidal at a concentration of 0.05-0.1% against *Candida albicans, Staphylococcus aureus* and *Pseudomonas aeruginosa* [10].

Chemical information [11]

Synonyms	Octenidine hydrochloride; N, N'-[Decane-1,10-diyldi-1(4H) pyridyl-4-ylidene] bis(octylammonium) dichloride
Molecular formula	C36H64Cl2N4
Molecular weight (g/mol)	623.83
IUPAC name	N-octyl-1-[10-(4-octyliminopyridin-1-yl) decyl] pyridin-4-imine dihydrochloride
CAS number	70775-75-6

Table a

Spectrum of activity

It has broad antimicrobial spectrum both against gram negative, gram positive bacteria as well as MRSA [12]. It also shows broad antimicrobial activity against bacteria responsible for plaque formation such as *Streptococcus species, Actinomyces, Mycoplasma, Chlamydia* [13].

Effect on biofilm development

Suppression of biofilm formation of S. *Aureus* strains can be achieved by Octenidine Dihydrochloride at 0.31-0.62% that needs at least 10 minutes of exposure time. This exposure can result to 0-25% of biofilm formation in comparison to no treatment. For inhibition of biofilm formation on the materials used in the oral cavities a concentration of atleast 3% is required [14]. As per a study conducted by Pitten FA., *et al.* (2003), CHX proved to be superior as compared to Octenidine and Povidone iodine against Streptococcus sanguis grown on hydroxyapatitie discs [15]. Shapiro S., *et al*. (2002) stated that the CHX, hexitidine and Octenidine are equally effective against plaque and show equal biofilm clearing and plaque-reducing activity [16]. As per study conducted by Bartoszewicz M., *et al.* (2007), Octenidine is significantly effective against the biofilms formed on the medical implants on comparison with Gentamicin [17].

Efficacy

Various species of bacteria like *E. Coli* has low MIC value of 0.25–8 mg/l, *E faecalis* has 4-16 mg/l, S. *aureus* has 0.25-9.3mg/l, *P. aeruginosa* has 1-8 mg/l and *S. pneumoniae* has a value of 8-32 mg/l for OCT meaning susceptible strains or isolates. Few oral species like S mutans has a MIC value of 120 mg/l, S Salivarius has 800 mg/l, meaning that these species are less susceptible for OCT [18]. When combined with 2% phenoxyethanol, 0.1% OCT provides a broad bactericidal activity just within 1 minute. Within 5 minutes of exposure with 0.01% OCT can provide a sufficient bactericidal activity against *S. aureus, E. Coli, K. pneumonia* etc. As per various studies, a bactericidal effect is seen within 10 mins of exposure at concentrations of 5 and 27 mg/l for *E. Coli* and *P. aeruginosa* respectively. In case of the presence of Albumin, the efficacy of the OCT is decreased by 0.75% [19]. Its *in vitro* antimicrobial potency is three- ten times greater as compared to CHX. It has a tremendous residual effect. Along with the direct antimycotic effect, it also causes alterations in the sterol and lipid content of the Candids albicans. It also effects the binding of the Candida Albican to the buccal epithelium [20]. As per a study conducted by Hübner N., *et al.* (2001), the MIC values of OCT for *E. coli, C. albicans*, *P. mirabilis*, *P. aeruginosa* and *S. aureus* are much lesser when compared with the values of CHX [21].

Efficacy as a mouthwash

Mouthwash containing OCT on comparison with CHX, is similarly effective on oral pathogens like *F. nucleatum, S. mutans,* and *Candida albican* as per study conducted by Rohrer N., *et al.* (2010) [22]. A reduction in the salivary bacterial count was seen by 3.7, 3.7 and 4.2 log after rinsing with 0.1, 0.15 and 0.2% for 1 minute as per a study conducted by Lorenz K., *et al.* (2018) [23]. 0.1% OCT along with 2% phenoxyethanol decreased the bacterial load of saliva by 2.8 log as per a study conducted by Pitten F., *et al.* (1999). Numerous other studies also showed that 0.1% OCT has good bactericidal effect [24].

Mechanism of action

OCT is believed to work by disrupting the cell membrane. It strongly binds to negatively charged microbial surfaces and to lipid components causing disruption of the cell membrane [25]. It binds to the surface of the bacteria because of the electrostatic interactions following penetration through lipopolysaccharide layer. There is interference of Hydrocarbon chains of Octenidine with fatty acyl chain of outer membrane core due to hydrophobic interactions, leading to entire lipid disorder that is based on the hydrophobic mismatch. Also, the molecules of Octenidine penetrates into the inner membrane from the outer side by the periplasmatic space, thus in an analogue manner, influence its integrity. Bacteria gets lysed within a short period of time [26].

Residual effect

Octenidine does not get absorbed percutaneously and binds to surfaces that are negatively charged. Hence, residues of the Octenidine stays at the application site leading to sustained antimicrobial effect [27].

Other applications

Can be used for the antisepsis before procedures that include skin-penetration. For example prior to the placement of the venous or arterial catheters, punctures, surgical procedures etc. Combination of Octenidine along with the aliphatic alcohol are available in the market for this purpose. This combination is provided so that there is sustained and prolonged antimicrobial effect unlike the immediate effect of the alcohols. For eliminating the microorganisms like methicillin-resistant Staphylococcus aureus (MRSA), that are antibiotic resistant and that colonize the skin, liquid soaps incorporated with Octenidine are used as shampoo or a shower gel. On intact mucosa, OCT is mainly used as single substance or OPE i.e., approved by Medical Devices of Germany and Fedral Institute for Medicinal Products for short period, repeated antiseptic treatment of mucosa. It is also approved for using before the surgical procedures, around the areas where surgery is to be performed in the oral cavity and anogenital areas. It can also be used for the treatment of the wounds [21]. It is used to prevent or treat the local infections mostly in the form of liquids or gel. Also used for washing the hands by medical staff as well as by the patients. Along with the phenoxyethanol, 0.1% OCT serves as a great antimicrobial agent that can be used to treat traumatic, acute and infected wounds that are colonized by multi-resistant strains. Gel formulations of OCT is particularly suitable in cases of burns and is considered as a better option than PVP-I. Also, it has been confirmed that it is quite safe for use among pregnant, breast-feeding women, premature babies and newborns. It can also be used for coating tracheostomy tubes and has proved to be effective in reducing the infection. Surgical sutures can also be coated by OCT [28].

Safety

The cytotoxicity rate is quite low for fibroblasts as well as for human epithelial cells, unlike as seen in case of CHX. It does not penetrate across the mucous membranes, wounds, skin and placental barrier unlike the antiseptics that are alcohol based, favours its use among premature babies, pregnant ladies and new borns. [28].

Contraindications

Recommended for external use only and should not be used for injections, Should not be used for peritoneal cavity rinsing, administration to the CNS structure should not be done [28].

Conclusion

Octenidine, introduced more than 20 years back is an effective antiseptic agent that is used in different fields and has the potential to replace various well known antiseptics like PVP-I, CHX or triclosan. Its popularity among the clinicians is increasing, as it is chemically stable with no reported resistant development, has low toxicity and is comparatively safe. Various studies have proved its efficacy in the field of dentistry. However, more clinical studies need to be conducted to know the efficacy of its different concentrations, substantivity, interactions with other anti-infective substances as well as to know the interaction with the tissue components [28].

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