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The Efficacy and Safety of Chlorhexidine in Nosocomial Infections

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Abstract: *Chlorhexidine is a common skin antisepsis agent that is also found in toothpaste and mouthwash. When mixed with alcohol, it is a particularly efficient antibacterial. Because it forms a strong bond with amino acid subunits in the peripheral skin and mucosal layers. Its antibacterial properties remain for a long time, enabling it to be an efficacious antiseptic agent. Chlorhexidine is applied on various medical devices which provide protection against various internal infections caused by catheter. Chlorhexidine-related contact dermatitis is uncommon among healthcare employees.in individuals where the incidence of allergic reactions is very common, the rate of skin allergic reactions caused by chlorhexidine ranges from 3.5 to 6.5 percent. Chlorhexidine induced allergic reactions are frequently misdiagnosed, leading to underreporting.*

Key Words: Chlorhexidine, Acute Hypersensitivity, Contact Dermatitis, Intravascular Access, Nosocomial Infections

Introduction

Imperial Chemical Industries (Manchester, UK) produced chlorhexidine as an antiseptic in the 1950s.(Davies, 1954 #121). Chlorhexidine is a common antiseptic agent in medical treatment, as well as a component of personal hygiene products like mouthwash and toothpaste. (Lim, 2008 #122).

Chemistry

Chemical Formula: 1:6-di[4-Chlorophenyldiguanido]-Hexane

It is a bis biguanide comprised of 2 chloroguanide-chains interlinked by an intertwined chain of hexamethylene. At pH=7, it is chemically found to be a base of strong nature, as well as a di-cation. It is naturally hydrophobic; thus it is conjugated with acids (e.g., gluconic or acetic acid) to pertain hydrophilic characteristics in its chemical nature and form Di gluconate or diacetate salts. Its liquid solutions are found to be apparently colorless, with no distinct odor, and with a bitter taste. The N-chlorinated chlorhexidine derivatives bind via covalent bonds to amino acid subunits in the peripheral skin and mucosa when they are applied through topical application, resulting in a long-lasting antibacterial action with little systemic absorption, even after oral administration. (Boyce, 2002 #55) (Rushton, 1977 #125).

Mechanism of Action

When administered in bacteriostatic doses, the site of action of Chlorhexidine is cell wall of the bacterium where is adsorbs on the phosphate-

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containing protein components. This binding is followed by entrance of the drug inside the bacteria which ultimately leads to breakdown of the bacterial cytoplasmic membrane. The drug creates irreversible precipitates with intracellular ATP and nucleic acids. (Kolasiński, 2019 #126).

Apart from its bacteriostatic effect, it is abundantly used as a bactericidal, fungicidal, fungistatic, and viricidal. Chlorhexidine is scientifically found to have a relatively greater molecular binding affinity for the cell wall of Gram-positive bacteria compared to Gram negative-bacteria. (Davies, 1954 #121).

Various Antiseptic Agents Using in Clinical Practice

Iodine is frequently used as an antiseptic in clinical practice Iodine is frequently marketed as an iodophor, which is an iodine containing solution along with surfactants or povidone. Povidone iodine, a ten percent iodophor solution with one percent accessible iodine, is the most used iodophor. e. Cysteine oxidation is caused by iodine molecules entering microbial cell walls, amino acid iodination, and unsaturated fatty acid oxidation. As a result, protein synthesis is reduced, and bacterial cell walls are damaged (Cowen, 1979 #43)(Gottardi, 2001 #129). Antisepsis alcohols include isopropanol, ethanol, and n-propanol. Alcohol causes cell lysis and poor cellular metabolism by coagulating and denaturing proteins in the cytoplasmic membranes. (Fendler, 2002 #130). because proteins are not easily denatured in the absence of water, alcohol's antimicrobial effect is greatest at alcohol concentrations of 60 to 95 percent with water.

Chlorhexidine in Clinical Settings

Oral Hygiene

Significantly used as an integral ingredient in mouthwashes, as well as dental gels and toothpaste. (Axelsson, 1993 #132), inhibiting the production of dental plaque and exerting an everlasting bacteriostatic effect.(Nguyen, 2015 #133).

Hand Antisepsis

Nosocomial infection is linked to In the superficial skin layer, staphylococcus aureus and gramme negative bacilli are found in a temporary hand flora. In the deeper skin layers, indigenous flora (coagulase negative staphylococcus epidermidis) is less likely to be harmful. (Boyce, 2002 #55). Antiseptic methods result in a reduction in germs. Alcohol-based hand rubs are the most effective at reducing the number of bacteria on personnel's hands, followed by antiseptic soaps and detergents, and non-antimicrobial soaps. Chlorhexidine-based solutions are used to give surgical hand antisepsis ('scrubbing').(Mulberrry, 2001 #135). The efficacy of cutaneous antisepsis is assessed in log reductions of bacterial counts, with a 1-log reduction indicating a 10-fold decrease in bacterial counts (removal of 90% of bacteria) and a 2-log reduction indicating a 100-fold decrease (elimination of 99 percent of bacteria) (Pereira, 1997 #136) Antimicrobial effectiveness guidelines set by the US Food and Drug Administration recommend a 1-log drop in bacterial counts after 1 minute, a 2-log reduction after 5 minutes, and a 3-log reduction after 10 minutes(Boyce, 2002 #55).

Iodine, alcohol, and chlorhexidine are the most often used antiseptics. The commencement of action of alcohol preparations is the quickest, followed by chlorhexidine, and finally povidone iodine. Chlorhexidine, on the other hand, has the highest residual antibacterial action. Chlorhexidine plus alcohol formulations combine the quick onset of alcohol with the long-lasting effects of chlorhexidine. (Lim, 2008 #138 Surgical skin preparation reduces the usual skin flora count prior to skin incision, which reduces surgical wound infection.s. Chlorhexidine alone, on the other hand, did not meet the bacterial count decrease criteria at 10 minutes).

Venipuncture

In case of topical formulations before venipuncture in a multicenter randomized trial, For skin preparation prior to venipuncture, alcoholic chlorhexidine 0.5 percent was compared to povidone iodine 10 percent For skin

preparation prior to venipuncture, alcoholic chlorhexidine 0.5 percent was compared to povidone iodine 10 percent. Blood cultures were less contaminated with alcoholic chlorhexidine (14/1019 cultures [1.4 percent] vs. 34/1022 cultures [4.4 percent. (Chaiyakunapruk, 2002 #143). In the management of vascular catheter sites, chlorhexidine with alcohol was utilized, chlorhexidine with alcohol was utilized instead of povidone iodine., a meta-analysis of eight randomized studies (including 4143 catheterizations) found a 50% risk decrease (1 vs. 2%). The sustained antibacterial activity of chlorhexidine, as well as its efficiency in the presence of fibrin and blood, helped to reduce the danger. (Chaiyakunapruk, 2002 #143).

Central Venous Catheters

Bacterial colonization and catheter-related infections are reduced with antibacterial-coated intravascular catheters. To prevent extraluminal contamination, Extraluminally coated central venous catheters Chlorhexidine breaks the bacterial cell membrane, allowing silver ions to enter the bacterial cell and attach to the DNA helix, preventing bacterial multiplication. (Mermel, 2001 #145). (Logghe, 1997 #146). The antimicrobial chemicals in the catheter seep into the surrounding tissue, limiting bacterial colonization of the entrance site and the transmission of bacteria from skin to catheter. (Wang, 2021 #147).

Disposition of Epidural Catheter

To limit the risk of epidural infections, antiseptic treatment is used to prepare the skin prior to inserting epidural catheters. Studies on epidural catheterization have used bacterial colonization rates on the tips of catheter as the endpoint, although mixed results have been reported in this regard. Using 0.4% chlorhexidine as compared to 10.0% povidone iodine as an antiseptic agent for skin, preceding epidural implantation was examined in a randomized research comprising 100 pediatric patients. Out of 44, the iodine group had 5 colonized catheter tips (5.6 per 100 catheter days) as compared to 1 colonized catheter tip out of 53 (0.5 per 100 days of the catheter) in the group i-e chlorhexidine (Rose, et al., 2019). Another randomized trial compared 0.5% chlorhexidine in ethanol to 10% povidone iodine for the skin preparation, preceding epidural insertion of the catheter in 90 gynecology surgical patients and found no significant difference in the rate of colonization in epidural catheter (positive culture site 8/34 [24 percent] in the chlorhexidine group vs 7/26 [25 percent] in the povidone iodine group) (Brookes et al., 2020).

Bacterial colonization at the catheter site may be reduced, which could prevent the bacterial tracking along the way to the epidural catheter thereby, reducing the occurrence of an epidural infection. Urethane dressing patch (Biopatch , Texas, Arlington) in a controlled randomized trial was applied to the sites of epidural insertion in order to lower the colonization rates in the catheter. The dressing Biopatch lowered the incidence of the colonized tips of the catheter (9/31 [29%] of the control group vs 1/26 [3.8%] of a colonized group where P = 0.06). A controlled randomized trial illustrated Biopatch group rate (11/26 [42.3%] vs 1/29[3.5%], P = 0.001) (Brookes et al., 2020).

Other Uses

- Chlorhexidine pre-operative baths have been recommended to decrease surgical wound infections.
- Three trials including a randomized, double-blind and a multi-centered controlled trial (including over 12,000 patients), failed to show that a complete urine catheterization regimen reduced the rates of postoperative wound infections.
- However, during an extended urinary catheterization, the bladder irrigation with 0.005% chlorhexidine prevented many urinary tract infections.

Adverse Effects

Chlorhexidine has few adverse effects. Between 1967 and 1984, sixty adverse reactions were

outlined to the Japanese Ministry of Welfare, in1968 and 2000, 16 adverse reactions were reported to the Danish Medicines Agency and between 1965 and 1996,182 were reported to the United Kingdom's Committee on Safety of the Medicines (Rose, et al., 2019). Despite of the fact that chlorhexidine is most commonly used in the dental care products, harmful effects such as tooth discoloration, formation of salivary dirt and calculus and transitory nullification of the sensation of taste are common.

Oral Administration

Mostly the orally administered chlorhexidine is normally well-tolerated due to the lack of systemic absorption but excessive dosages can induce deleterious effects. Fed formula which is commonly administered and prepared by adding 0.05% chlorhexidine. 1 of the patients developed acute pulmonary oedema and four developed oral ulcers and oedema of the tongue. An 80-year-old woman died of acute respiratory distress syndrome after accidently ingesting 10 g chlorhexidine (20 ml of 5% solution). Ingestion of 0.3 g of chlorhexidine induced lobular hepatitis and generalized fatty degeneration of the liver in a patient who attempted to commit suicide (Wand et al., 2017).

Intra-articular Irrigation

During a knee arthroscopy, an erroneous intra-articular treatment with aqueous 1 percent chlorhexidine caused persistent discomfort, edoema, crepitus, and stiffness.

Corneal Damage

Prevention of any contact between eyes of the employees and patients and chlorhexidine preparations should be given a priority. 4% Chlorhexidine generated an acute stromal edema in animal studies. Chlorhexidine has been linked to corneal injury during cataract surgery while preparing for the pre-surgical skin treatment, ethmoidectomy, face reconstructive surgery, craniotomy, blepharoplasty as well as the accidental spillage into the eye. In ophthalmological preparations, lower doses of the chlorhexidine are employed without causing toxicity and harm.

Intra-venous Administration

In three patients, unintentional intravenous chlorhexidine injection was documented in a review of chlorhexidine toxicity. Two individuals experienced haemolysis, which was linked to the solution's hypotonicity. In another case, a 67-year-old male patient was unintentionally given an intravenous infusion of 0.8 mg chlorhexidine gluconate, which treated extracorporeal membrane oxygenation and plasma exchange successfully in cases of severe hypoxemia (Steinsapir & Woodward, 2017).

Diathermy Burns

Because of the alcoholic content, solutions containing alcohol and chlorhexidine have been known to cause diathermy burns. According to one case study, the incontinence pads used in patients largely absorb alcohol-chlorhexidine mixture, and cause ignition when diathermy is applied.

Ototoxicity

Chlorhexidine damages the middle and inner part of the ear. Deafness following myringoplast has been linked to pre-operative ear disinfection with chlorhexidine. When chlorhexidine was administered in the middle ear in an animal study, it caused damage to the cochlea and vestibular nerve, as well as the loss of auditory and vestibular functions.

Skin Reactions

In very low birth weight newborns, chlorhexidine impregnated dressings are linked to localized skin responses. In a controlled randomized study, 200 newborns were given a chlorhexidine gluconate impregnated bandage as compared to povidone for the central venous site catheter care. The researcher suggested that low birth weight infants' susceptibility to various skin reactions was

heightened by the thinner stratum corneum, and decreased cohesiveness between the epidermis and dermis of the skin (Wand et al., 2017).

The skin reactions are related to chlorhexidine skin sterilization swabs, 0.05% irrigation solution of chlorhexidine commonly employed before inserting a skin 'prep' solutions which is used befor the surgery through an intrauterine contraceptive device. At Danish skin clinic, the occurence of contact dermatitis was 1.5% in patch tested patients with 1% gluconate chlorhexidine. The frequency of contact dermatitis with 1% chlorhexidine gluconate is 6.4% in atopic patients (Chiewchalermsri et al., 2020).

Acute Hypersensitivity Reaction

Chlorhexidine is a potential cause of anaphylactic shock and other hypersensitivity reactions. The use of chlorhexidine for urological catheterization, as an antiseptic for skin surgery, central venous catheters chlorhexidine-coated, insertion of epidural catheters, over-the-counter skin antiseptics, lubricant gel and as a skin antiseptic for mucous membranes has all been linked to acute hypersensitivity reactions. Chorhexidine reactions usually occur during anesthesia or surgery.

Chlorhexidine anaphylaxis incidence was reported in 1967 and 1984 in Japan. In 1988, he Danish Anaesthesia Allergy Centre was established. The center investigated 37 subjects suffering from anaphylactoid reactions due to the use of Chlorhexidine. 4 out of 22 patients had positive tests to all the agents peri-operatively also depicted positive hypersensitive reactions to the chlorhexidine drug (Chiewchalermsri et al., 2020).

Topical chlorhexidine commonly applied to mucosal surfaces can also cause anaphylaxis. The 50 cases of adverse reactions to chlorhexidine reported to the Japanese Ministry of Welfare between 1967 and 1984 included nine cases of anaphylactic shock, all of which were linked to mucosal application of the drug. As a result, the Japanese Ministry of Welfare advised against using chlorhexidine on the mucous membranes. A case study from Australia documented an abrupt hypersensitive reaction to chlorhexidine administered to the vaginal mucosa at the end of surgery in the post-anesthetic care unit.

When administered to the skin, chlorhexidine can produce several acute hypersensitivity reactions. Several cases of intra-operative anaphylaxis to the chlorhexidine have been documented, and the researchers emphasized the necessity of addressing chlorhexidine as the leading cause of anaphylaxis during the surgery due to widespread sources of chlorhexidine sensitization such as in throat lozenges and skin creams. At least 22 incidences of anaphylaxis have been linked to the use of chlorhexidine-containing urethral lubricating gel during urinary catheterization. Anaphylaxis can be caused by urethral lubricants, which are frequently neglected.

Chlorhexidine is used in a variety of wound dressings. Anaphylaxis has been reported to be caused by dressings coated with acetate of chlorhexidine per 10 g.

Chlorhexidine Sensitization

In health-care professionals, the risk of sensitization and allergy to the drug is low. There are no positive reactions among 105 health-care workers who completed skin prick, skin patch, and intra-dermal testing in Danish study that looked into the prevalence of various types of hypersensitivity including type I and type IV hypersensitivity reactions. In dermatology patients, type IV allergy to chlorhexidine occurs in 1 to 2.5 percent of the cases (Noor et al., 2016). Because transdermal absorption of chlorhexidine is limited, sensitization to chlorhexidine mostly occurs after mucosal exposure than after hand washing. According to a case report, three nurses acquired asthma after being exposed to the surface cleaning spray comprising of alcohol and chlorhexidine. FEV1 decreased in challenge test with aerosol. When the aerosol was stopped, the asthmatic symptoms disappeared (Wand et al., 2017).

Conclusion

When compared to other iodine preparations, chlorhexidine is one of the most effective skin antiseptic that retains antibacterial activity in blood, resulting in faster and long-lasting reduction in the bacterial growth rate. The use of chlorhexidine for the skin preparations and chlorhexidine-coated catheters can help to decrease central venous catheter infections. Although devastating adverse events to the drug are rarely reported, chlorhexidine is rather uncommon yet an un-recognized cause of the anaphylaxis and other hypersensitive reactions. Chlorhexidine is ototoxic and causes ocular damage hence it should be avoided coming into contact with the cornea and the middle ear.

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