Undesirable Effects of Some Topical Antiseptics

Chemical, pharmacological and dermatological aspects

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Topical antiseptics are a diverse group of agents that are widely used in medicine for the antimicrobial properties. Despite their long history and broad application, caution must be exercised in their use, especially in the pediatric age group, as various cutaneous reactions ranging from hypersensitivity to urticarial to skin necrosis have been reported. The use of topical antiseptics in pediatrics has also been associated with systemic reactions, which depend on the antiseptic in question. Antiseptics such as chlorhexidine, povidon iodine, methylene blue, gentian violet, silver nitrate, boric acid, Castellani solution, alcohol and chloramines have been reviewed. It is essential that physicians bear in mind the possible adverse effects that may follow topical antiseptic use, as this facilitates prevention and also timely intervention if, and when, they occur.

Keywords:antiseptics,adverse effects,children

Topical antiseptics are widely used in medicine. Recently published papers are raising questions with regard to antiseptic usage in children cutaneous pathology and associated contact dermatitis. This review will be focused on topical antiseptics and their adverse reactions, with a view to identifying the best options for antiseptic usage in children

Topical antiseptics

Chlorhexidine

Chlorhexidine (CH) is a biguanide used as an antiseptic agent and has topical antibacterial activity. Chlorhexidine, $C_{22}H_{30}Cl_2N_{10}$ is (1E)-2-[6-[[amino-[(E)-[amino-(4-chloroanilino)methylidene]amino]methylidene]amino] hexyl]-1-[amino-(4-chloroanilino) methylidene]guanidine (fig. 1). Chlorhexidine is a symmetrical molecule. It has four chlorophenyl rings and two bisguanide groups connected by a central hexamethylene bridge[1].

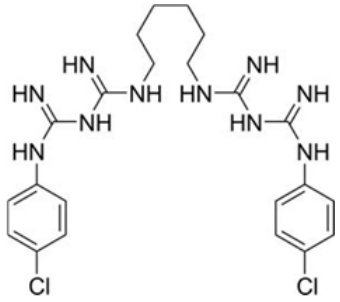

Fig. 1. Chemical structure of chlorhexidine

Chlorhexidine is positively charged and reacts with the negatively charged microbial cell surface, thereby destroying the integrity of the cell membrane. Subsequently, chlorhexidine penetrates into the cell and causes leakage of intracellular components leading to cell death. Since gram positive bacteria are more negatively charged, they are more sensitive to this agent.

Only a few cases of clorhexidine contact dermatitis have previously been described in the literature but a recent article[2] revealed a sensitisation potential of clorhexidine in children. Although the population was small (n=14), up to 11 patients (~78%) showed positivity for chlorhexidine on contact allergy testing with the European baseline series. Chlorhexidine use in newborns may cause burns in some cases, thereby predisposing them to sepsis, excessive water loss, hypothermia and renal failure[3]. But we have to be more cautious when using clorhexidine on skin, mucous membranes or other external areas.

Chlorhexidine is also a product used in the manufacture of toothpaste or mouthwash;and fixed drug eruption has been reported after use of mouthwash [4]. Chlorhexidine(CH) showed ototoxicity related to contact time and concentrations used if it reaches the inner ear [5]. The results from a study on cats showed that CH is ototoxic exerting effects on the sensory cell-nerve ending complex of the labyrinthine vestibule [6].IgE levels may be used to demonstrate allergy to chlorhexidine. Chlorhexidine-specific IgE levels >0.35KUA/L appears to be the levels at which chlorhexidine allergy can be conclusively shown to have occurred. Optimum sampling time appears to be between 1-4 months. The authors noted, however, that levels <0.35KUA/L could not be used to rule out hypersensitivity to chlorhexidine [7]. Patients with eczema, especially those with leg ulcers or leg eczema, are especially prone to chlorhexidine allergies [8].Anaphylactic reactions have been reported after the use of chlorhexidine including during normal bladder catheterization [9,10].Irreversible corneal injuries and opacification attributed to chlorhexidinegluconate 4% topical preparation, are reported in 4 female patients, aged 9 months to 83 years, in whom the drug was accidentally introduced into the eye during surgical preparation. One patient responded to atropine and corticosteroids. A second patient required a corneal transplant [11].

Anaphylaxis may follow topical application of chlorhexidinegluconatesolution.The causative agent of type I hypersensitivity by intradermal, scratch; and epicutaneous tests was found to be chlorhexidine gluconate in a 6-patient series. Such life-threatening adverse reactions, to chlorhexidinegluconate may be averted by using it on wound surfaces at a concentration of 0.05%, chlorhexidinegluconate may not be suitable for application to mucous membranes [12].

Many alcohol products include low levels of chlorhexidine, which remains on the skin following evaporation of the alcohol, or excipients, which decrease

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the evaporation time of the alcohol and can significantly increase product efficacy[13].

Alcohol and CH had a toxic effect on cochlear and the vestibular function of the inner ear of the sand rat but povidone-iodine did not based on recordings of vestibular evoked potentials and auditory brainstem response [6, 14].

Alcohol

Alcohol produces injury to cells by dehydration and precipitation of the cytoplasm or protoplasm. Little is known about the specific mode of action of alcohols,but based on the increased efficacy in the presence of water, itis generally believed that they cause membrane damage and rapid denaturation of proteins, with subsequent interferencewith metabolism and cell lysis [13]. This accounts for its bactericidal and antifungal action.Although much less rare side effects after using alcohol as an antiseptic, sometimes real reactions have been reported after using this antiseptic..A conclusive study conducted in the US on medical staff using alcohol for hand disinfection revealed that 3 out of 4 people studied developed allergic skin reactions [15].

Povidone-iodine

Povidone-iodine(PVP-I) is safer than CH solution,which should not used on the scalp or on facial area as the literature revealed cases of severe chlorhexidine-related irreversible keratitis.

Povidone-iodine, $C_6H_9I_2NO$, (1-ethenylpyrrolidin-2-one;molecular iodine)is a stable chemical complex of polyvinylpyrrolidone(povidone, PVP) and elemental iodine(fig. 2). It contains from 9.0 to 12.0% available iodine, calculated by dry weight.

Povidone-iodine is an example of an iodophor, a complex of molecular iodine and asolubilizing carrier (polyvinylpyrrolidone), which acts as a reservoir of *free* active iodine that is constantly released and remains in dynamic equilibrium with the complex. Povidone-iodine is available in a range of antiseptic formulations (solution, scrub, ointment, tincture, and foam) the aqueous solution is (10% PVP-I) the most commonly used [16].

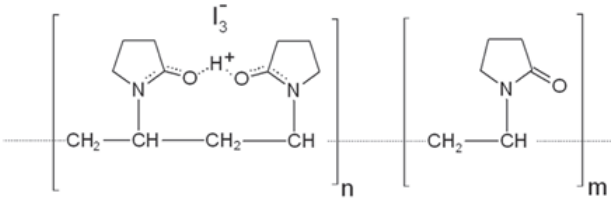

Fig. 2.Chemical structure of povidone-iodine (PVP-I)

Povidone iodine is a kind of iodinedisinfectant, which directly causes *in vivo* protein denaturation, precipitation of bacteria, further resulting in the death of pathogenic microorganisms. Therefore, it is effective in disinfection and sterilization. It can kill viruses, bacteria, spores, fungi, and protozoa with low toxicity to humans. Povidone-iodine aqueous solution has strong pharmacological activity against *Staphylococcus aureus, Neisseria gonorrhoeae, Pseudomonas aeruginosa*, syphilis, hepatitis B virus, HIV, and *Trichomonas vaginalis* [17].

There are also reports about contact dermatitis after povidone iodine usage in surgery and the results of patch tests with 10% povidone iodine in petrolatum were positive [18]. Due to increased risk of allergic dermatitis to PVP-I following prolonged contact, some authors recommend preoperative tests for PVP-I allergy in all patients[19].

Boric acid

Another antiseptic solution is boric acid aqueous solutions. Boric acid, trihydroxyborane, (H_3BO_3) is a weakly acidic hydrate of boric oxide with mild antiseptic, antifungal, and antiviral properties. The exact mechanism of action of boric acid is unknown; generally cytotoxic to all cells. It is used in the treatment of yeast infections and cold sores [20].

A case of allergic contact dermatitis from a condensate of boric acid, monoethanolamine and fatty acids in a metalworking fluids and also association of reversible alopecia with occupational topical exposure to common borax-containing solutions were described in a case series reports [21, 22]. A case of toxic dermatitis has been reported after using 2% boric acid in a 2-year-old girl. Due to its rapid absorption and slow elimination, boric acid presents an increased risk of systemic side effects. On the other hand, local side effects are not reported in the literature [23]. Dermatologic effects are more common after chronic or subacute exposures. Skin changes may develop after boric acid ingestion or application of boric acid powder. Erythema and desquamation occurs in 1 to 2 days. Exfoliation that is generalized or localized to the hands, feet or face may occur and has been termed the boiled lobster syndrome. Erythema may be prominent on the buttocks and scrotum [24, 25].

Castellanisolution

When locally applied to the middle ear cavity of the rat, Castellanisolution does not affect distortion product otoacoustic emission amplitudes so is not ototoxic and even more it was a simple and effective as topical application for the treatment of granular myringitis with good antiseptic results on *Staphylococcus, Coryneba cterium* and Providenciastuartii [26, 27]. A study on rats observed that Castellanisolution is safer than Burow's solution for external otitis and otomycosis when the perforation of tympanic membrane is done [28].

Methylene blue

Methylene blue (MB), is [7-(dimethylamino) phenothiazine-3-ylidene]-dimethylazanium; chloride.The chemical structure of MB, $C_{16}H_{18}N_3ClS$, includes three joined rings of atoms(figs. 3) [29].

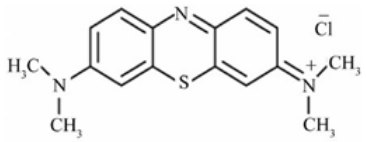

Fig. 3. Chemical structure of methylene blue dye (MB)

MB andGentian Violet (GV) organic dyes have oxidation–reduction (redox) potentials in the range of many electron transport components of oxidative metabolism, and it has been suggested that these dyes operate by *short circuiting* electron transport pathways. Bacteria need a certain level of balance between reductive and oxidative actions to be able to survive. Studies have shown that MB/GV alter this environment to make bacterial life unsustainable.Both MB and GV dyes are basic with a positive charge, thus showing differential activity toward gram-negative versus gram-positive bacteria [30].

MB is a common antiseptic but as a chromophore dye it is also known for its photosensitizing properties. These have been described especially during MB assisted parathyroid surgery when a Light-Emitting Diode (LED) type of lamp was used [31, 32]. A rare case of hypersensitivity reaction to MB has been reported during lip reconstruction surgery with anaphylactic shock to MB [33]. Methylene blue-treated

fresh-frozen plasma (MB-FFP) is mainly used in Europe. The combined action of methylene blue and illumination is a photodynamic process that prevents replication of RNA and viral DNA. The first immediate allergic reaction to plasma-transfusion treated with methyl blue was reported. Clinical course and subsequent evaluation of the allergic reaction, including skin tests and basophil activation test, confirmed Methyl-Blue IgE-mediated anaphylaxis [34]. A recent study on a number of cases has demonstrated a previously unrecognized, significant interaction between serotonin reuptake inhibitors and methylene blue as the conclusion of this study is that serotonin syndromes may interact with methyl blue, causing a serious adverse reaction consistent with serotonin syndrome [35]. Methylene blue is also used for the detection of sentinel nodes when there is no possibility of using Technetiu 99 and in case of using methyl blue as a tracer for the sentinel gland in breast cancer or breast cancer, skin allergic reactions have been reported to shock anaphylactically requiring pre-interventional testing of methyl blue in all these patients [36].

Six cases of immediate breast reconstruction using implants were complicated by methylene blue dye. One case of local infection was improved by conservative treatment. In two cases, partial necrosis and wound dehiscence of the incision areas were observed; thus, debridement and closure were performed. Of the three cases of wide skin necrosis, two cases underwent removal of the dead tissue and implants, followed by primary closure. In the other case, the breast implant was salvaged using latissimus dorsi musculocutaneous flap reconstruction. The complications were caused by MBD toxicity, which aggravated blood disturbance and skin tension after implant insertion [37].

Silver nitrate

Silver nitrate is a widely used antiseptic also used in different concentrations for cauterizing and wound healing properties. $AgNO_3$Silver ion reacts with the thiol group in vital enzymes and inactivates them [38, 39] or interacts with DNA, resulting in marked enhancement of pyrimidine dimerization by photodynamic reaction and possible prevention of DNA replication [39-41]. Structural changes in the cell envelope and the presence of some small electron-dense granules formed with silver and sulfur have also been demonstrated in bacterial [42,43]. It can also produce allergic and toxic reactions in various concentrations [44]. Silver nitrate is sometimes used and intrapleural injection where it can cause an increase in blood levels of LDH and IL-8 as well as blood VEGF [45]. Adverse reactions to silver nitrate have also been reported after use in Credé syndrome when cutaneous burns have been reported [46]. Three infants treated for umbilical granuloma with silver nitrate suffered chemical burns to the periumbilical area which prompted visits to the emergency department [47].

The phototoxic effect of MB associated with silver nanoparticles suggests that the association has potential as a Photodynamic Therapy agent [48].

Gentian violet

Gentian violet, $C_{25}H_{30}ClN_3$ is a blue, aniline-derived dye with antifungal and antimitotic properties [48].Gentian violet is[4-[bis[4-(dimethylamino) phenyl] methylidene] cyclohexa-2,5-dien-1-ylidene]-dimethylazanium;chloride (fig. 4).

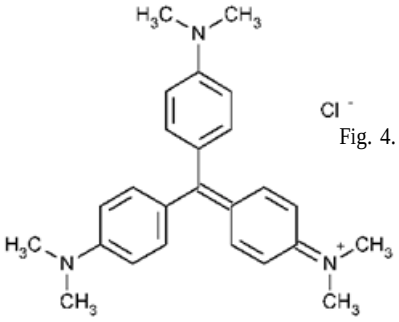

Fig. 4. Chemical structure of gentian violet

Gentian Violet is a blue, aniline-derived dye with antifungal and antimitotic properties. Gentian violet (GV) dissociates into positive (GV+) and negative ions (Cl-) that penetrate both gram-positive and gram-negative bacterial cells. The GV+ ions interact with negatively charged components of the bacterial cell wall including lipopolysaccharide,peptidoglycan and DNA. This agent is also a mutagen and mitotic poison. GV elicits a photodynamic action mediated by a free-radical mechanism. Furthermore, this agent dissipates the action potential on prokaryotic or eukaryotic membranes by inducing permeability, thereby leading to respiratory inhibition and subsequent cell death[49].

Gentian Violet is a weak sensitizer when used as an antiseptic therapeutic dye, except when used on ulcers and eczematized skin. Gentian Violet may produce not only allergic contact dermatitis but also necrosis in the interiginous areas [50].

A 57-year-old female with eczema on her left ankle developed dermatitis when she used Gentian Violet as treatment. Patch tests with 1% Gentian Violet solution on normal skin were negative for 48 h. After 72 h, follicular lesions appeared that turned into a papulonodular, nonvesicular dermatitis. Intradermal tests with 0.02% Gentian Violet were positive. After 24 h, a mild itching dermatitis with follicular swelling was present covering an area of 2 cm in diameter after 48 h [50].

Investigators described a case in which a 2-year-old male developed a necrotic skin reaction in the gluteal fold after application of 2% Basic Violet 3 in aqueous solution to treat diaper dermatitis. After discontinuation of the solution, demarcation of the necrotic area and reepithelization of the wounded surfaces occurred [50].

The authors describe a patient who developed superficial necrosis of the glans penis from irritation after topical treatment with 1% gentian violet. The foregoing condition resolved after withdrawal of treatment. A differential diagnosis (sexually transmitted diseases, epidermoid carcinoma, etc.] is warranted on finding this type of lesion in the glans penis[51].

Chloramines

Chloramines (chlorine and ammonia) are used routinely to disinfect and sterilize potable water.These chemical substances are intensively used for cleaning and disinfection in industry and hospital[52]. N-Chloramines have been used as antimicrobial agents in such commercial products as laundry bleaches and industrial sanitizing compounds and in the disinfection of sewage. Their inhibitory activities are of a broad spectrum, including interference with both glucose oxidation and ionic exchange and the disruption of the cell membrane [53, 54].

Research to date indicates that chloramines primarily inactivate microorganisms by irreversible denaturation of proteins and to a lesser extent by denaturation of the nucleic acids. Chloramine inactivation of bacteria is caused primarily by the oxidation of sulfhydryl-containing enzymes and, to a lesser extent, a reaction with the nucleic acid. There are no existing data to suggest that chloramines

can modify the permeability state of the cell. Viral inactivation by chloramines is believed to result from its reaction with either the protein coat or the nucleic acid [55- 57].High blood levels of chloramines are associated with hemolysis and rarely methemoglobinemia. Uremic patients have a decreased ability to withstand oxidative stress. It is postulated that their antioxidant capacity is reduced, yet the mechanism remains unclear.

Patients on maintenance hemodialysis are vulnerable to chloramine toxicity if chloramines are inadequately removed from water[58]. A case of allergic contact urticaria due to chloramine was described[59]. The reason simple chlorination had to be abandoned in many water districts was because it created unacceptable amounts of trihalomethanes (THM's). THM's, including chloroform ($CHCl_3$), dichlorobromo-methane ($CHCl_2Br$), chlorodibromo-methane ($CHClBr_2$) and bromoform ($CHBr_3$) are formed from the interaction of chlorine with natural organics of vegetable origins (hydrocarbons, humic acid, etc.) and naturally occurring bromide. THM's are carcinogenic and teratogenic[60-62].

Like any other oxidant entering the bloodstream, chloramine will cause oxidative damage to red cells and to other systems. In low doses, the first manifestation will be methemoglobinemia. The next stage is a Heinz body anemia, in which red blood cells (RBCs) damaged by oxidation are recognized, sequestered, and destroyed by the spleen. The worst manifestation is acute intravascular hemolysis, when there is dark blood in the dialyzer lines, and the patient may have acute dyspnea, malaise, headaches, palpitations, vomiting, and rapidly developing anemia. Low-grade chloramine exposure could be missed [63].

Conclusions

Antiseptics are used in various medical and surgical conditions [64-72]. Their role is to inhibit the bacterian,viral pathologic proliferation but also they act by inhibing normal microbiota or endosymbionts[73-83]. It is useful to inform the parents of the children about the possible adverse reactions and the informed consent should be signed by them [84, 85]. Children's skin is more susceptible to absorbtion of external substances-including antiseptics-due its thinner stratum corneum and favourable ratio between weight and skin surface area.We consider that water and soap for umbilical cord care seems sufficient to prevent septic risk in industrialized countries [2].

Plant extracts with limited side effects potential should be used in selected cases, especially in *Locus minorisresistentiae* cutaneous areas [86-89]. Maybe a consensus on appropriate antiseptic solutions in dermatology would minimize possible medicolegal actions and our patients'suffering and risks.

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Manuscript received: 14.01.2019