WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 8, 1653-1665. Editorial Article ISSN 2277– 7105

SODIUM 1,5–DICHLORO–4,6–DIOXO–1,4,5,6–TETRAHYDRO–1,3,5–TRIAZIN–2–OLATE AS BROAD SPECTRUM FAST ACTING SANITIZER AND WATER STERILIZER

***Prof. Dr. Dhrubo Jyoti Sen**

Department of Pharmaceutical Chemistry, Shri Sarvajanik Pharmacy College, Gujarat Technological University, Arvind Baug, Mehsana–384001, Gujarat, India.

Article Received on
20 June 2016,

Revised on 10 July 2016,
Accepted on 01 August 2016

DOI: 10.20959/wjpr20168-6944

***Corresponding Author**
Prof. Dr. Dhrubo Jyoti Sen
Department of Pharmaceutical Chemistry, Shri Sarvajanik Pharmacy College, Gujarat Technological University, Arvind Baug, Mehsana –384001, Gujarat, India.

ABSTRACT

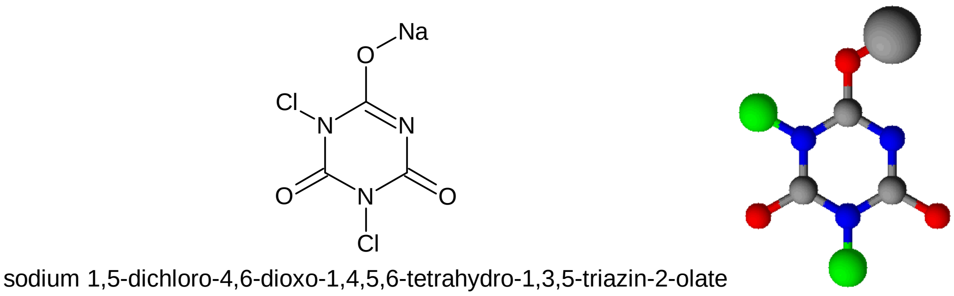
Household water treatment using sodium hypochlorite (NaOCl) has been recognized as a cost–effective means of reducing the heavy burden of diarrhoea and other waterborne diseases, especially among populations without access to improved water supplies. Sodium dichloroisocyanurate (NaDCC), which is widely used in emergencies, is an alternative source of chlorine that may present certain advantages over NaOCl for household–based interventions in development settings. Like other sources of hypochlorous acid, NaDCC has been shown to be an effective antimicrobial agent. The chemical composition and physical characteristics of NaDCC tablets, however, may offer certain advantages over NaOCl as a possible donor of free chlorine in the disinfection of water at the household level. The safety of the compound for the routine treatment of drinking water has now been satisfactorily addressed. There is also evidence that suggests that use of NaDCC tablets increases compliance and is more acceptable and affordable than NaOCl thus potentially increasing overall uptake in a household–based water treatment intervention. These advantages would have to be balanced against its relative lack of availability compared to NaOCl and the issues that this raises about its sustainability. While there is reason to believe that NaDCC may present a promising alternative to NaOCl in household based water treatment interventions, it has yet to be subjected to the same kinds of rigorous trials to which NaOCl and certain other point–of–use interventions have been subject. Longer–term randomized, controlled trials in different settings in which NaDCC is compared not only against a control group without access to water treatment but also directly against an intervention group using NaOCl would help clarify its potential benefits, including

microbiological effectiveness, compliance, acceptability and affordability. Some of these questions can also be explored in the assessment of pilot programs. Investigators should also determine the programmatic support necessary to achieve a given level of coverage in order to assess its cost–effectiveness. This research would not only address remaining issues about the possible role of NaDCC tablets as a public health intervention, but also provide useful information to determine if investment that would be necessary to bring the intervention to scale on a sustainable basis would be warranted.

KEYWORDS: Chlorine, Household, NaDCC, Sodium hypochlorite, Sodium dichloroisocyanurate, Water treatment.

OVERVIEW

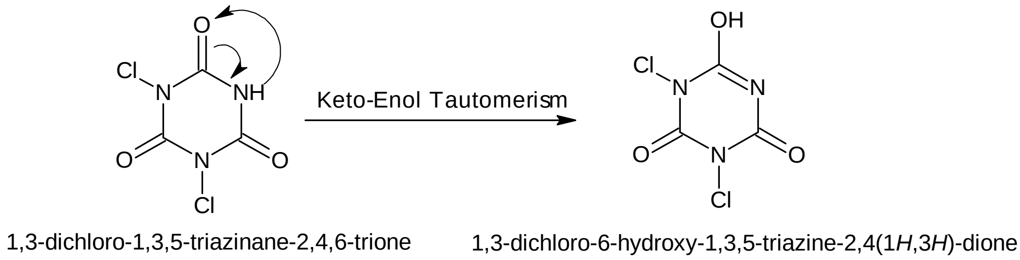
1,3,5–Triazine–2,4,6(1*H*,3*H*,5H)–trione, 1,3–dichloro–, sodium salt, Sodium 3,5–dichloro–2,4,6–trioxo–1,3,5–triazinan–1–ide, Sodium dichloroisocyanurate, Sodium troclosene, Sodic troclosene as Ef–Chlor (NaDCC tablet) is a broad spectrum fast acting sanitizer and water sterilizer, rapidly effective against **bacteria, viruses, fungi and protozoa**. Total spectrum of activity i.e. effective against hydro hypophilic viruses, gram positive & gram negative bacteria, fungi mould, yeast, mycoplasmas & protozoa.[1]



Figure–1: Ef–Chlor or NaDCC

Molecular Formula=$C_3Cl_2N_3NaO_3$, Formula Weight=219.94 g/mol, Composition=C (16.38%), Cl (32.24%), N (19.10%), Na (10.45%), O (21.82). Appearance white, crystalline powder, Odor chlorine–like, Density 0.7 g/cm^3 (as granules), Melting point=225°C (437°F; 498 K), Solubility in water=22.7 g/100 mL (25°C), Solubility in acetone 0.5 g/100 mL (30°C), Acidity (pKa) 6.2–6.8. The sodium salt of 1,5–dichloro–4,6–dioxo–1,4,5,6–tetrahydro–1,3,5–triazin–2–olate (NaDCC) in aqueous solution produces 1,3–dichloro–6–hydroxy–1,3,5–triazine–2,4(1*H*,3*H*)–dione which is phenolic compound which undergoes *vice–versa* keto–enol tautomerism to

1,3–dichloro–1,3,5–triazinane–2,4,6–trione. The pKa range of phenolic compound shows 6.2–6.8 range due to acidic pH due to enol functional group. It melts at high temperature due to sodium salt.[2]



Figure–2: Tautomeric approach of Ef–Chlor or NaDCC

Applications

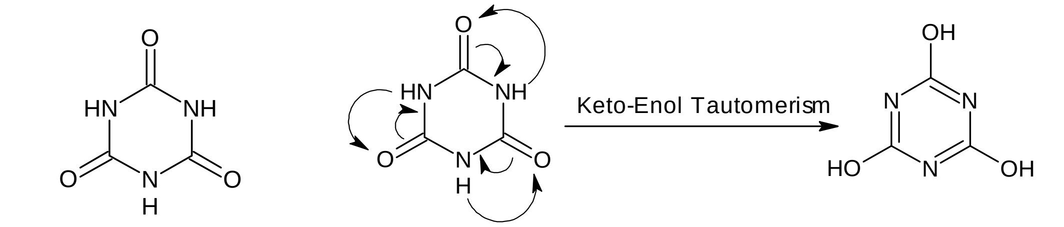
Drinking Water Purification, Hospital Disinfection, Baby Bottle Sterilizing, Janitorial Cleaning, Food and Catering, Fruit and vegetable disinfection, Poultry. For fast treatment of water for: Emergency and Disaster, Travel and Camping, Household, Peace Keeping/Defence Forces, Marine Application, Disinfection of Water System, Municipal Water supplies.

Advantages

Recommended by leading infection control experts worldwide. Effective against virtually all known bacteria, viruses and spores. Safe to handle and store. Compact storage and transport reducing transport costs. Economic and Accurate – no under or over dosing. Greater Biocidal Effect – Rapid release of HOCl encouraging fast biocidal activity forming clear disinfecting solution. More environmentally friendly than alternative disinfectants. Fast Dissolving and ready to use quickly. Stable tablets with 3 year shelf life. Available in a wide selection of tablet strengths. Resistant to organic spoilage.[3]

Sodium dichloroisocyanurate (INN: sodium troclosene, troclosenum natricum or NaDCC or SDIC) is a chemical compound widely used cleansing agent and disinfectant. It is a colorless, water–soluble solid. The dihydrate is also known (51580–86–0) as is the potassium salt (2244–21–5). It is mainly used as a disinfectant, biocide, industrial deodorant and detergent. It is found in some modern water purification tablets/filters. It is more efficient than formerly used halazone water disinfectant. In these applications, it is a source of slow release of chlorine in low concentrations at a relatively constant rate. As a disinfectant, it is used to sterilize drinking water, swimming pools, tableware and air, fight against infectious diseases as routine disinfection. It can be used as a preventive for disinfection and environmental sterilization, in raising silkworm, livestock, poultry and fish and also can be used to prevent wool from shrinking, bleaching textiles and cleaning industrial circulating water. In one notably interesting experiment, a concentrated solution of NaDCC and a dilute solution of copper (II) sulphate are mixed, producing an intense lilac precipitate of the complex salt sodium copper dichloroisocyanurate. The reactions between Dichloroisocyanurate salts (Na, K, Li, Ba, Ca) and transition metal salts (Ni, Cu, Cd) are described in patent US 3'055'889. The overall reaction is: $CuSO_4 + 4\ Na(C_3N_3O_3Cl_2) \rightarrow Na_2[Cu(C_3N_3O_3Cl_2)_4] + Na_2SO_4$

It is used to show chemiluminescence as it emits red light upon decomposition by concentrated (130 vol, 35%) hydrogen peroxide. Cyanuric acid or 1,3,5–triazine–2,4,6–triol is a chemical compound with the formula $(CNOH)_3$. Like many industrially useful chemicals, this triazine has many synonyms. This white, odorless solid finds use as a precursor or a component of bleaches, disinfectants and herbicides. In 1997, worldwide production was 160 million kilograms. Cyanuric acid is used as a chlorine stabilizer in swimming pools. It binds to free chlorine and releases it slowly, extending the time needed to deplete each dose of sanitizer. The antineoplastic alkylating agent, teroxirone, is formed by reacting cyanuric acid with 3 equivalents of epichlorohydrin.



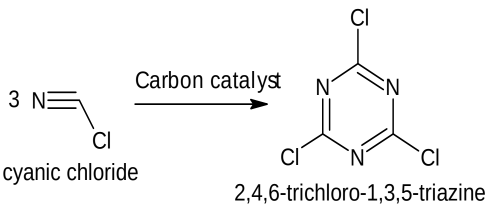
Figure–3: Tautomeric approach of Cyanuric acid

Precursors to chlorinated cyanurates: Cyanuric acid is mainly used as a precursor to N–chlorinated cyanurates, which are used to disinfect water. The dichloro derivative is prepared by direct chlorination:

$[C(O)NH]_3 + 2\ Cl_2 + 2\ NaOH \rightarrow [C(O)NCl]_2[C(O)NH]$

This species is typically converted to its sodium salt, sodium dichloro–s–triazinetrione. Further chlorination gives trichloroisocyanuric acid, $[C(O)NCl]_3$. These N–chloro compounds serve as disinfectants and algaecides for swimming pool water. It stabilizes the chlorine in the pool and prevents the chlorine from being quickly consumed by sunlight. Precursors to cross linking agents: Because of its tri–functionality, CYA is a precursor to cross linking agents, especially for polyurethane resins. Impure copper salt of the acid, with the formula $Cu(C_3N_3O_3H_2)_2(NH_3)_2$, is currently the only known isocyanurate mineral, called joanneumite. It was found in a guano deposit in Chile. It is very rare. Cyanuric chloride is an organic compound with the formula $(NCCl)_3$. This white solid is the chlorinated derivative of 1,3,5–triazine. It is the trimer of cyanogen chloride. Cyanuric chloride is the main precursor to the popular but controversial herbicide atrazine. Cyanuric chloride is prepared in two steps from hydrogen cyanide via the intermediacy of cyanogens chloride, which is trimerized at elevated temperatures over a carbon catalyst:

$HCN + Cl_2 \rightarrow ClCN + HCl$



Figure–4: Cyanuric chloride preparation

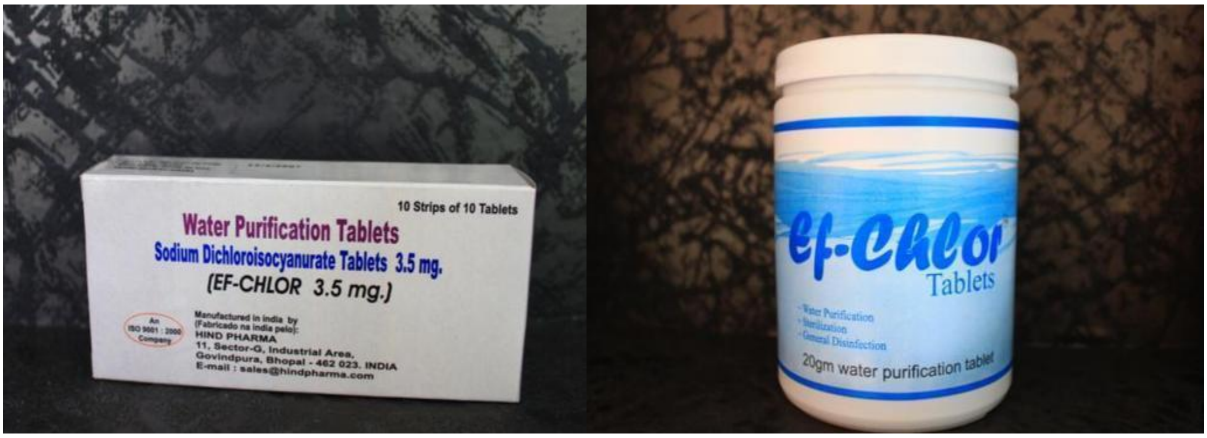
It is estimated that 70% of cyanuric chloride is used in the preparation of the triazine–class pesticides, especially atrazine. Such reactions rely on the easy displacement of the chloride with nucleophiles such as amines:

$(ClCN)_3 + 2\ RNH_2 \rightarrow (RNHCN)(ClCN)_2 + RNH_3 + Cl^-$

Other triazine herbicides, such as simazine, anilazine and cyromazine are made in an analogous way. Cyanuric chloride is also used as a precursor to dyes and cross linking agents. The largest class of these dyes is the sulfonated triazine–stilbene optical brighteners (OBA) or fluorescent whitening agents (FWA) commonly found in detergent formulas and white paper. Many reactive dyes also incorporate a triazine ring. They are also manufactured by way of the chloride displacement reaction shown above.[4]

Hypochlorites, the most widely used of the chlorine disinfectants, are available as liquid (e.g., sodium hypochlorite) or solid (e.g., calcium hypochlorite). The most prevalent chlorine products in the United States are aqueous solutions of 5.25%–6.15% sodium hypochlorite, usually called household bleach. They have a broad spectrum of antimicrobial activity, do not leave toxic residues, are unaffected by water hardness, are inexpensive and fast acting, remove dried or fixed organisms and bio–films from surfaces and have a low incidence of serious toxicity. Sodium hypochlorite at the concentration used in household bleach (5.25–6.15%) can produce ocular irritation or oropharyngeal, esophageal and gastric burns.

Other disadvantages of hypochlorites include corrosiveness to metals in high concentrations (>500 ppm), inactivation by organic matter, discoloring or "bleaching" of fabrics, release of toxic chlorine gas when mixed with ammonia or acid (e.g., household cleaning agents) and relative stability. The microbicidal activity of chlorine is attributed largely to undissociated hypochlorous acid (HOCl). The dissociation of HOCl to the less microbicidal form (hypochlorite ion OCl^{-}) depends on pH. The disinfecting efficacy of chlorine decreases with an increase in pH that parallels the conversion of undissociated HOCI to OCl^{-}. A potential hazard is production of the carcinogen bis (chloromethyl) ether when hypochlorite solutions contact formaldehyde and the production of the animal carcinogen trihalomethane when hot water is hyper chlorinated. After reviewing environmental fate and ecologic data, EPA has determined the currently registered uses of hypochlorites will not result in unreasonable adverse effects to the environment.[5]



Figure–5: Ef–Chlor

Alternative compounds that release chlorine and are used in the health–care setting include demand–release chlorine dioxide, sodium dichloroisocyanurate and chloramine–T. The advantage of these compounds over the hypochlorites is that they retain chlorine longer and so exert a more prolonged bactericidal effect. Sodium dichloroisocyanurate tablets are stable, and for two reasons, the microbicidal activity of solutions prepared from sodium dichloroisocyanurate tablets might be greater than that of sodium hypochlorite solutions containing the same total available chlorine. First, with sodium dichloroisocyanurate, only 50% of the total available chlorine is free (HOCl and OCl^{-}), whereas the remainder is combined (monochloroisocyanurate or dichloroisocyanurate) and as free available chlorine is used up, the latter is released to restore the equilibrium. Second, solutions of sodium dichloroisocyanurate are acidic, whereas sodium hypochlorite solutions are alkaline and the more microbicidal type of chlorine (HOCl) is believed to predominate. Chlorine dioxide–based disinfectants are prepared fresh as required by mixing the two components (base solution [citric acid with preservatives and corrosion inhibitors] and the activator solution [sodium chlorite]). *In–vitro* suspension tests showed that solutions containing about 140 ppm chlorine dioxide achieved a reduction factor exceeding 106 of *S.aureus* in 1 minute and of *B.atrophaeus* spores in 2.5 minutes in the presence of 3 g/L bovine albumin. The potential for damaging equipment requires consideration because long–term use can damage the outer plastic coat of the insertion tube 534. In another study, chlorine dioxide solutions at either 600 ppm or 30 ppm killed *M.avium*–intracellular within 60 seconds after contact but contamination by organic material significantly affected the microbicidal properties. The microbicidal activity of a new disinfectant, "super oxidized water," has been examined The concept of electrolyzing saline to create a disinfectant or antiseptics is appealing because the basic materials of saline and electricity are inexpensive and the end product (i.e., water) does not damage the environment.[6] The main products of this water are hypochlorous acid (e.g., at a concentration of about 144 mg/L) and chlorine. As with any germicide, the antimicrobial activity of super oxidized water is strongly affected by the concentration of the active ingredient (available free chlorine) 536. One manufacturer generates the disinfectant at the point of use by passing a saline solution over coated titanium electrodes at 9 amps. The product generated has a pH of 5.0–6.5 and an oxidation–reduction potential (redox) of >950 mV. Although super oxidized water is intended to be generated fresh at the point of use, when tested under clean conditions the disinfectant was effective within 5 minutes when 48 hours old. Unfortunately, the equipment required to produce the product can be expensive because parameters such as pH, current and redox potential must be closely monitored. The solution is nontoxic to biologic tissues. Although the United Kingdom manufacturer claims the solution is noncorrosive and non–damaging to endoscopes and processing equipment, one flexible endoscope manufacturer (Olympus Key–Med, United Kingdom) has voided the warranty on the endoscopes if super oxidized water is used to disinfect them. As with any germicide formulation, the user should check with the device manufacturer for compatibility with the germicide. Additional studies are needed to determine whether this solution could be used as an alternative to other disinfectants or antiseptics for hand washing, skin antisepsis, room cleaning, or equipment disinfection (e.g., endoscopes, dialyzers). In October 2002, the FDA cleared super oxidized water as a high–level disinfectant (FDA, personal communication, September 18, 2002).

Figure–6: Effervescent tablets of water purifier

Mode of Action

The exact mechanism by which free chlorine destroys microorganisms has not been elucidated. Inactivation by chlorine can result from a number of factors: oxidation of sulfhydryl enzymes and amino acids; ring chlorination of amino acids; loss of intracellular contents; decreased uptake of nutrients; inhibition of protein synthesis; decreased oxygen uptake; oxidation of respiratory components; decreased adenosine triphosphate production; breaks in DNA; and depressed DNA synthesis. The actual microbicidal mechanism of chlorine might involve a combination of these factors or the effect of chlorine on critical sites.

At 25°C and atmospheric pressure, one liter of water dissolves 3.26 g or 1.125 L of gaseous chlorine. Chlorine dissolves in water to produce dissolved chlorine (Cl_2) and by reversible reaction, hydrochloric acid and hypochlorous acid: $Cl_2 + H_2O \rightleftharpoons HCl + HClO$.

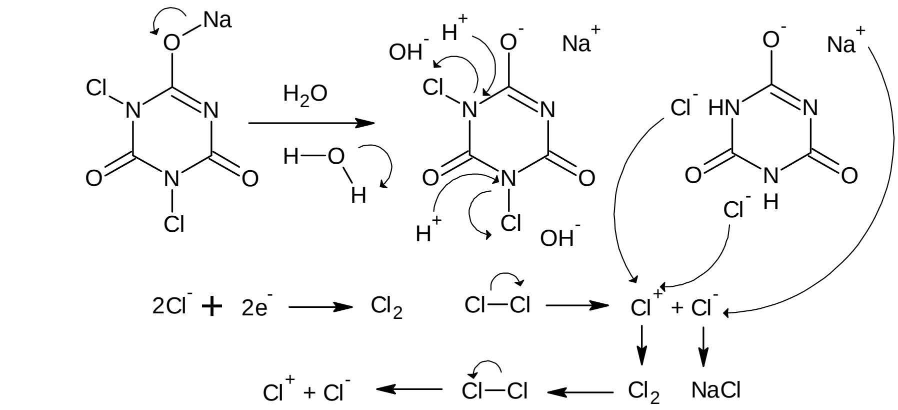
The conversion to the right is called disproportionation because the ingredient chlorine both increases and decreases in formal oxidation state. The solubility of chlorine in water is increased if the water contains dissolved alkali hydroxide and in this way, chlorine bleach is produced: $Cl_2 + 2\ OH^- \rightarrow ClO^- + Cl^- + H_2O$. Dissolved elemental chlorine gas is present only in a neutral or acidic solution.[7]

Microbicidal Activity

Low concentrations of free available chlorine (e.g., HOCl, OCl^- and elemental chlorine–Cl_2) have a biocidal effect on mycoplasma (25 ppm) and vegetative bacteria (<5 ppm) in seconds in the absence of an organic load. Higher concentrations (1,000 ppm) of chlorine are required to kill *M.tuberculosis* using the Association of Official Analytical Chemists (AOAC) tuberculocidal test. A concentration of 100 ppm will kill ≥99.9% of *B.atrophaeus* spores within 5 minutes and destroy mycotic agents in <1 hour. Acidified bleach and regular bleach (5,000 ppm chlorine) can inactivate 106 *C.difficile* spores in <10 minutes. One study reported that 25 different viruses were inactivated in 10 minutes with 200 ppm available chlorine. Several studies have demonstrated the effectiveness of diluted sodium hypochlorite and other disinfectants to inactivate HIV 61. Chlorine (500 ppm) showed inhibition of Candida after 30 seconds of exposure. In experiments using the AOAC Use–Dilution Method, 100 ppm of free chlorine killed 106–107 *S.aureus*, *S.choleraesuis* and *P.aeruginosa* in <10 minutes. Because household bleach contains 5.25%–6.15% sodium hypochlorite, or 52,500–61,500 ppm available chlorine, a 1:1,000 dilution provides about 53–62 ppm available chlorine and a 1:10 dilution of household bleach provides about 5250–6150 ppm. Data are available for chlorine dioxide that supports manufacturers' bactericidal, fungicidal, sporicidal, tuberculocidal and virucidal label claims. A chlorine dioxide generator has been shown effective for decontaminating flexible endoscopes but it is not currently FDA–cleared for use as a high–level disinfectant. Chlorine dioxide can be produced by mixing solutions, such as a solution of chlorine with a solution of sodium chlorite. In 1986, a chlorine dioxide product was voluntarily removed from the market when its use caused leakage of cellulose–based dialyzer membranes, which allowed bacteria to migrate from the dialysis fluid side of the dialyzer to the blood side.[8]

Sodium dichloroisocyanurate at 2,500 ppm available chlorine is effective against bacteria in the presence of up to 20% plasma, compared with 10% plasma for sodium hypochlorite at 2,500 ppm. "Super oxidized water" has been tested against bacteria, mycobacteria, viruses, fungi and spores. Freshly generated super oxidized water is rapidly effective (<2 minutes) in achieving a reduction of pathogenic microorganisms (i.e., *M.tuberculosis*, *M.chelonae*, poliovirus, HIV, multidrug–resistant *S.aureus*, *E.coli*, *C.albicans*, *E.faecalis*, *P.aeruginosa*) in the absence of organic loading. However, the biocidal activity of this disinfectant decreased substantially in the presence of organic material (e.g., 5% horse serum). No bacteria or viruses were detected on artificially contaminated endoscopes after a 5–minute exposure to super oxidized water and HBV–DNA was not detected from any endoscope experimentally contaminated with HBV–positive mixed sera after a disinfectant exposure time of 7 minutes.

$$Cl_2 + 2e^- \longrightarrow 2Cl^-$$



Figure–7: Mode of action

Chlorine is a strong oxidizing agent because it absorbs two electrons to be oxidized into two chloride anions (Cl^-). It is released from sodium dichloroisocyanurate in aqueous solution and recombines into molecular chlorine (Cl_2) which reacts with water to form hypochlorous acid which acts as a disinfectant. Hypochlorous acid is a weak acid with the chemical formula HOCl. It forms when chlorine dissolves in water and itself partially dissociates in water, into hypochlorite (–) and hydronium ions (+). It is HOCl and OCl– that are the primary agents for disinfection when chlorine is used to disinfect water for human use. It cannot be isolated in pure form due to rapid equilibration with its precursor. HClO is an oxidizer and in its sodium salt form sodium hypochlorite (NaClO), or in its calcium salt form calcium hypochlorite ($Ca(ClO)_2$), can be used as a bleach, a deodorant and a disinfectant.[9]

Uses. Hypochlorites are widely used in healthcare facilities in a variety of settings. 328 Inorganic chlorine solution is used for disinfecting tonometer heads and for spot–disinfection of countertops and floors. A 1:10–1:100 dilution of 5.25%–6.15% sodium hypochlorite (i.e., household bleach) or an EPA–registered tuberculocidal disinfectant 17has been recommended for decontaminating blood spills. Tonometry is the procedure eye care professionals perform to determine the intraocular pressure (IOP), the fluid pressure inside the eye. It is an important test in the evaluation of patients at risk from glaucoma. Most tonometers are calibrated to measure pressure in millimeters of mercury (mmHg). For small spills of blood (i.e., drops of blood) on noncritical surfaces, the area can be disinfected with a 1:100 dilution of 5.25%–6.15% sodium hypochlorite or an EPA–registered tuberculocidal disinfectant. Because hypochlorites and other germicides are substantially inactivated in the presence of blood large spills of blood require that the surface be cleaned before an EPA–registered disinfectant or a 1:10 (final concentration) solution of household bleach is applied. If a sharps injury is possible, the surface initially should be decontaminated then cleaned and disinfected (1:10 final concentration). Extreme care always should be taken to prevent percutaneous injury. At least 500 ppm available chlorine for 10 minutes is recommended for decontaminating CPR training manikins. Full–strength bleach has been recommended for self–disinfection of needles and syringes used for illicit–drug injection when needle–exchange programs are not available. The difference in the recommended concentrations of bleach reflects the difficulty of cleaning the interior of needles and syringes and the use of needles and syringes for parenteral injection. Clinicians should not alter their use of chlorine on environmental surfaces on the basis of testing methodologies that do not simulate actual disinfection practices. Other uses in healthcare include as an irrigating agent in endodontic treatment and as a disinfectant for manikins, laundry, dental appliances, hydrotherapy tanks regulated medical waste before disposal and the water distribution system in hemodialysis centers and hemodialysis machines. Chlorine long has been used as the disinfectant in water treatment. Hyperchlorination of a Legionella–contaminated hospital water system resulted in a dramatic decrease (from 30% to 1.5%) in the isolation of *L.pneumophila* from water outlets and a cessation of healthcare–associated Legionnaires' disease in an affected unit. Water disinfection with monochloramine by municipal water–treatment plants substantially reduced the risk for healthcare–associated Legionnaires disease. Chlorine dioxide also has been used to control Legionella in a hospital water supply. Chloramine T and hypochlorites have been used to disinfect hydrotherapy equipment. Hypochlorite solutions in tap water at a pH >8 stored at room temperature (23ºC) in closed, opaque plastic containers can lose up to 40%–50% of their free available chlorine level over 1 month. Thus, if a user wished to have a solution containing 500 ppm of available chlorine at day 30, he or she should prepare a solution containing 1,000 ppm of chlorine at time 0. Sodium hypochlorite solution does not decompose after 30 days when stored in a closed brown bottle. The use of powders, composed of a mixture of a chlorine–releasing agent with highly absorbent resin, for disinfecting spills of body fluids has been evaluated by laboratory tests and hospital ward trials. The inclusion of acrylic resin particles in formulations markedly increases the volume of fluid that can be soaked up because the resin can absorb 200–300 times its own weight of fluid, depending on the fluid consistency. When experimental formulations containing 1%, 5% and 10% available chlorine were evaluated by a standardized surface test, those containing 10% demonstrated bactericidal activity. One problem with chlorine–releasing granules is that they can generate chlorine fumes when applied to urine.[10]

CONCLUSION

It is clear that microorganisms can adapt to a variety of environmental physical and chemical conditions and it is therefore not surprising that resistance to extensively used antiseptics and disinfectants has been reported. Of the mechanisms that have been studied, the most significant are clearly intrinsic, in particular the ability to sporulate, adaptation of pseudomonades and the protective effects of bio–films. In these cases, “resistance” may be incorrectly used and “tolerance,” defined as developmental or protective effects that permit microorganisms to survive in the presence of an active agent, may be more correct. Many of these reports of resistance have often paralleled issues including inadequate cleaning, incorrect product use, or ineffective infection control practices, which cannot be underestimated. Some acquired mechanisms (in particular with heavy–metal resistance) have also been shown to be clinically significant, but in most cases the results have been speculative. Increased MICs have been confirmed, in particular for staphylococci. However, few reports have further investigated increased bactericidal concentrations or actual use dilutions of products, which in many cases contain significantly higher concentrations of biocides, or formulation attributes, which can increase product efficacy; in a number of cases, changes in the MICs have actually been shown not to be significant. Efflux mechanisms are known to be important in antibiotic resistance, but it is questionable if the observed increased MICs of biocides could have clinical implications for hard–surface or topical disinfection. It has been speculated that low–level resistance may aid in the survival of microorganisms at residual levels of antiseptics and disinfectants; any possible clinical significance of this remains to be tested. With growing concerns about the development of biocide resistance and cross–resistance with antibiotics, it is clear that clinical isolates should be under continual surveillance and possible mechanisms should be investigated. It is also clear that antiseptic and disinfectant products can vary significantly, despite containing similar levels of biocides, which underlines the need for close inspection of efficacy claims and adequate test methodology. In addition, a particular antiseptic or disinfectant product may be better selected (as part of infection control practices) based on particular circumstances or nosocomial outbreaks; for example, certain active agents are clearly more efficacious against gram–positive than gram–negative bacteria and *C.difficile* (despite the intrinsic resistance of spores) may be effectively controlled physically by adequate cleaning with QAC–based products.

In conclusion, a great deal remains to be learned about the mode of action of antiseptics and disinfectants. Although significant progress has been made with bacterial investigations, a greater understanding of these mechanisms is clearly lacking for other infectious agents. Studies of the mechanisms of action of and microbial resistance to antiseptics and disinfectants are thus not merely of academic significance. They are associated with the more efficient use of these agents clinically and with the potential design of newer, more effective compounds and products.

REFERENCES

1. WHO. Guidelines for Drinking–Water Quality, Vol. 1, Recommendations. World Health Organization, Geneva, Switzerland, 1993.
2. Bloomfield S.F. Chlorine and iodine formulations. In: Ascenzi, J.M. (Ed.), Handbook of Disinfectants and Antiseptics. Marcel Dekker, Inc., New York, NY, 1996.
3. Bloomfield S.F. and Arthur M. Interaction of Bacillus subtilis spores with sodium hypochlorite, sodium dichloroisocyanurate and chloramine–T. J. Appl. Bacteriol. 1992; 72: 166–172.
4. Bloomfield S.F. and Miles G.A. The antibacterial properties of sodium dichloroisocyanurate and sodium hypochlorite formulations. J. Appl. Bacteriol. 1979; 46: 65–73.
5. Bloomfield S.F. and Uso E.E. The antibacterial properties of sodium hypochlorite and sodium dichloroisocyanurate as hospital disinfectants. J. Hosp. Infect. 1985; 6: 20–30.
6. Le Dantec C., Duguet J.P., Montiel A., Dumoutier N., Dubrou S. and Vincent V. Chlorine disinfection of atypical mycobacteria isolated from a water distribution system. Appl. Environ. Microbiol. 2002; 68: 1025–1032.
7. WHO. Evaluation of certain food additives and contaminants. World Health Report Tech Rep Ser. 922, 1–176, World Health Organization, Geneva, Switzerland, 2004.
8. D'Auria F.D., Simonetti G. and Strippoli V. Antimicrobial activity exerted by sodium dichloroisocyanurate. Ann. Ig. 1989; 1(6): 1445–1458.
9. Crump J.A., Otieno P.O., Slutsker L., Keswick B.H., Rosen D.H., Hoekstra R.M., Vulule J.M. and Luby, S.P. Household based treatment of drinking water with flocculant–disinfectant for preventing diarrhea in areas with turbid source water in rural western Kenya: cluster randomized controlled trial. BMJ, 2005; 331: 478–483.
10. Fewtrell L., Kaufmann R., Kay D., Enanoria W., Haller L. and Colford J. Water, sanitation and hygiene interventions to reduce diarrhoea in less developed countries: a systematic review and meta–analysis. Lancet Infect. Dis., 2005; 5: 42–52.