Chlorine Dioxide: Does it contribute to human health? A brief review

Bastidas-Ortiz, Humberto (Bas-Orh)[1]

January 31, 2021

Abstract

Chlorine dioxide, ClO_2, a non-patentable substance, is a molecule composed by two of the most disinfectant elements found in nature, chlorine and oxygen, both of them electronegative. As early as 1850, ClO_2 has been being used in the oxidation of water and, since 1944, in the treatment of waste water and the bleaching of cellulose. Similarly, oxygen, in the form of hydrogen peroxide, is used to disinfect ambulances, hospital rooms and medical equipment, among other applications. Recently, the Global Health and Life Coalition (GHLC) has reported favourable results in the treatment of COVID-19 using ClO_2 under a parameterized protocol design by scientists members of this organization. Other research works carried out in different parts of the world sustain the hypothesis that, as a relatively stable radical and as a highly oxidant regardless of the pH in its surroundings, ClO_2 and its application in an area so sensitive as human health presents itself as an alterntive worth studying further.

1 Introduction

Chlorine dioxide, ClO_2, was discovered by Humphry Davy in 1811 while mixing potassium chlorate and sulphuric acid. Davy named his discovery *euchlorine*[10]. This compound is a gas at tempertures no greater than 11°C, green-yellowish color, irritating, 2.4 times denser than air, which disolves easily in water but hardly reacts with it; furthermore, it is a molecule highly energetic, that works as an oxidant extremelly selective due to its unique one electron transfer mechanism [30, 2]. On the other hand, ClO_2 has the disadvantage of not being safely compressed nor stored commercially since it is explosive under pressure[2]. The utilization of ClO_2 began in Europe around 1850, when it started to be used in water treatment[6]. Its applications have expanded to the control of microbiological growth in industries such as dairy, beverages and fruits and vegetables; treatment of municipal waters, industrial waste waters and potable water; food industry such as food canning, swine and cattle in general[41]; control of flavors and odors, caused among others by chlorophenols and algae[30] and removal of iron and manganese as well[43]. In particular, ClO_2 is preferred over chlorine in the treatment of municipal waste waters since it is a much more effective disinfectant at a pH of 8.5, it is less prone to generate potentially carcinogenic trihalomethanes[42], such as chloroform, bromodichlorometane and dibromochlorometane[4], and its antibacterial effect changes little in relation to pH[6]. This last property is also stated by Hoigné & Bader[19], whom add that ClO_2 is favoured over chlorine because it produces less chlorinated organic substances (i.e. trihalomethanes, haloacids, dioxines, furanes)[15]), absolutely no chloroform and only negligible quantities of aldehydes, cetones, cetoacids or other problematic compounds associated with the oxidation of organic matter[43]. Likewise, Aieta & Berg[11] establish that purifcation of water using ClO_2 does not represent any health issue, neither chronic nor accute, and that it neither shows any indication of carcinogenic or mutagenic activity. Finally, both ClO_2 and hydrogen peroxide are used to disinfect spaces, equipment and furniture in health-care facilities[15, 3]; specifically, Gordon & Rosenblatt[15] report the disinfection of buildings contaminated with spores of *Antrax* using

[1]Retired Professor. Autonomous University of Sinaloa. Mexico. hub9orion@gmail.com

ClO_2. Recently, and during the severe crisis originated by COVID-19, Chen et al.[8] have used ClO_2 successfully as disinfectant and in the control of contamination of air, while both *Escherichia coli* and *Salmonella app.*, considered the pathogenes associated with infectious and transmissible human diseases most commonly found in ambient air in poultry farms, have been fought satisfactorily using ClO_2[1].

2 State of the Art

One of the properties of ClO_2 that most calls the attention of the scientific community is that this compound kills microbes quickly and without causing damages to humans nor animals[32], property that, according to Gordon et al.[16], is due to its mechanism of transfer of electrons which attacks centers rich in electrons in organic molecules, and reducing itself to chlorite ion in the process. In their studies about the kinetic mechanisms that the biological route of disinfection of ClO_2 might follow, Bernarde et al.[7] suggested in 1965 that its disinfection capacity and its strong oxidative quality might be based in the alteration that it exerts on the celular wall of the bacteria when it concentrates above normal residual leves in the protein coat, inducing it to release nucleic acid and proteins in the medium. This suggestion was confirmed and further developed later by Gray[30] in 2014 and by other studies, among others, those by Isaac et al.[22] whom investigated the kinetics and mechanisms of ClO_2 in the inactivation of *Escherichia coli* (ATCC 35218) finding out that the compound increased the permeability of both the external as well as the citoplasmic membranes of the bacteria generating, in this manner, the discharge of components of the membrane such as 260 nm absorvent materials and inhibiting the activity of the intracelular enzyme β-D-galactosidasa. Similarly, Berg et al.[5] report that ClO_2 alters the permeability of the external celular membrane, as suggested by measurements of the flow of potassium ions, and that the simultaneous inhibition of the breathing capacity is caused by the non specific destruction of the transmembrane ionic gradient. This increment in the permeability of the membrane and the alteration of proteins and lipids of the external membrane are brought about by ClO_2, add Olivieri et al[34] and Ghandbari et al[14]. Additionally, a key inactivation mechanism of ClO_2 is the degradation that it generates to celular physiological functions such as the synthesis of proteins, lipids and biomolecules specific to the celular wall and nucleic acids such as cysteine, triptophan and tyrosine[30]. This non-destructive effect of ClO_2 was also observed by Daniel et al.[9] whom, in an experiment with a control group of 300 Sprague-Dawley rats, administered dosages at different concentrations of chlorine, monochloramine and ClO_2 to the control group during 90 days with no rats dying to the ClO_2 at all. In addition, ClO_2 is more disinfectant at high levels of pH and this attribute is barely influenced by the initial density of bacteria [23]; moreover, it is known that an aqueous solution of ClO_2 is capable of inactivating any type of virus[20]. For instance, a value of CT (concentration in mg/L times the contact time in minutes) in the order of 8.4 mg/L X min is sufficient to inactivate viruses up to four orders of magnitude, that is, 99.99% in an aqueous medium at 25°C[12]. Also, the funcionality of the homotrimeric glycoprotein haemagglutinin found on the surface of influenza viruses (H1N1) can be suppressed by ClO_2, as a function of concentration, time and temperature, when it oxidates the triptophan derived from the central region of the receptor-binding site of haemagglutinin, disabling consequently its binding capacity to generate infection[33].

One more beneficial property of ClO_2 is that, when it decomposes in acid medium, it liberates active species (free radicals) of oxygen, which are very effective against microorganisms and infectious viruses. This property is favourable specially for adult persons since, as it is well known, the capacity of the inmune system in humans decreases with age [17] and with it its capacity to provide these active species of oxygen, making them more vulnarable to a large variety of viral infections and the appearance of strange symptoms in case of infection; even more, the biochemical mechanisms of ClO_2 are so fundamental that they inhibit the growth of resistant strains of bacteria and yeast [49]. Also, Isaac et al[23] indicate that some research works have found out that ClO_2 shows a strong potential in the oxidation and removal of pharmaceutical residues such as dicoflenac[48], tetracyclines[36] and sulfamethoxazole[46]´ in waste water.

3 Dose and concentration

"Each and every substance is a venom, there is no substance that is not a venom. The correct dose differentiates a venom out of a remedy.". Philippus Aireolus Theophrastus Bombastus von Hohenheim, swiss physician from the German Medieval, alchemist, teologist and philosopher also known as *Paracelso* (alike to Celso, roman physician from the first century), pronounced this phrase which is used frequently to establish that the toxicity of a chemical substance, either of natural or chemically synthetized source, is a function of the quantity in which it is ingested but not of its origin[39].

Caffeine is a psychotonic alkaloid naturally found in almost 60 species of plants such as, coffee, tea, cocoa, guarana and mate, being it the most consumed psychostimulant in the world nowadays[47]. Even though the ingestion of caffeine is considered safe at a dose of $\leq$ 400 mg/day in healthy adults[35], the former can not be considered an innocuous compound since it can cause toxicity or even death, more commonly through myocardial infarction or arrythmia, if it is consumed in high quantities; furthermore, a sub-lethal dose, $\approx$ 7-10 mg/kg in healthy adults, can cause chills, nauseas, headaches, palpitations and tremblings with variation in the intensity of the symptoms depending upon the sensibility of the subject[47]. On the other hand, a drastic example of the effect of concentration of a medicament or ingredient is the plant *Belladona*. Lee[26] report that, in a dose of 100 mg, the active ingredient of the plant, l-atropina, can cause death. However, that same plant, when processed by the homeopathic pharmaceutical industry and taken to an ultramolecular dilution (concentration) of 0C to 1000C, does not bring about death but redimes certain illnesses related to fiebers and swelling processes, among others[37]. It is a well-known fact that both dose and concentration of a medicament or active ingredient, together with other variables, are crucial to attain positive therapeutic effects and much has been said about the toxicity of ClO_2 in human consumption. However, Young[49] recounts that, when ClO_2 reacts as an anti-microbial agent, the atom of oxygen bonds first to a simple atom (that which is oxidated), dissosiates from chlorine and finally donates an electron to chlorine producing, in this way, a chlorite ion, a negligible quantity when it is understood that there are naturally 5.3 g/L of chlorite ions in the human plasma. Obviously, a chlorite ion is obtained per molecule of ClO_2 but, how much ClO_2 can be ingested safely? At this point, the Therapeutic Drug Monitoring (TDM), clinical practice that consists in quantify drugs at certain intervals to maintain a constant concentration in the bloodstream of the patient so that the individual dose regimes could be optimized, is used to monitor drugs in very narrow therapeutic ranges, drugs with a singular strong pharmakinetic variability, medicines for which the optimal concentrations are difficult to monitor and drugs known to have secondary effects[25]. Likewise, TDM is promoted under the assumption that there exist a definible relationship between drug dose and concentration in either plasma or in bloodstream as there exists between concentration and therapeutic effects[25]. ClO_2 falls in these last categories and few studies exist about the monitoring of the effects of concentration of ClO_2 ingested by human beings, so that its application has been being tuned up almost by trial and error in different areas. At present, it is known that some organic microcontaminants in waste waters oxidate at concentrations of ClO_2 of $\approx$ 4 mg/L, while steroid estrogens and industrial estrogenic chemicals are removed under doses of ClO_2 between 1.25 and 3.75 mg/L[18]; also, dilutions of up to 100 ppm are used to fight against *candidiasis*, while an incubation in tissue culture of ClO_2 with VIH-infested CD4+ lymphocytes neutralized the VIH virus with a minimal effect on the CD4+ cells[29]. Finally, it is stressed that the use of ClO_2 in human consumption has already been being studied several times. In 1981, Michael et al.[13] carried out an epidemiologyc study in a rural village in the USA, in which an experimental group consumed water disinfected with ClO_2 whereas a control group did not consume this water. 351 persons donated blood samples and provided information such as sex, age, water source, medical history, medication use, chronic and acute illnesses and water consumption habits. The content of chlorite ion on the treated water was ≈ 5 ppm. Hematologic and serum chemistry analyses were carried out on the blood samples. The experiment ran for 115 days. After this period, hematologic and serum chemisty analyses were performed again on the remaining subjects, 197 from the experimental group and 112 from the control group. A statistical analysis using three-variable ANOVA with a p value < 0.05 revealed that there were no significant health effects related to the exposure to ClO_2. As it is evident, the concentrations of ClO_2 used in different applications were well below the concentration of chlorite ions in the human plasma, 5.3 mg/L.

4 COMUSAV

The Global Health and Life Coalition (GHLC) is an organization of physicians present in 14 countries and which has promoted the use of ClO_2 in the treatment of coronavirus. The GHLC has published the document *Chlorine Dioxide: A safe and potentially effective solution to overcome COVID-19*[21] that provides undeniable scientific support to this alternative. There exists a GHLC chapter in Mexico, which has tried to sensitize government authorities in promoting the massive use of ClO_2 to no avail. Nevertheless, in multiple occasions GHLC representatives have publicly stressed their disposition to colaborate in the future with the body of governance in attending the serious public health problem derived from the COVID-19 pandemia.

5 Experiences in massive use

The massive use of ClO_2 has been being studied for some years now. Lubbers et al.[27] describe in 1982 the clinical application of chlorated water on a daily basis in an experimental group under three different phases. In the first phase, chlorated disinfectants in concentrations that increased progressively were administered to healthy adult male volunteers; in the second phase, chlorated disinfectants in concentration of 5 mg/L were ingested for 12 days to healthy subjects; finally, in phase three, chlorite in concentration of 5 mg/L was administered during 12 days to subjects in risk of suffering oxidative stress due to the defficiency of glucose-6-phosphate dehidrogenase. The results showed that there were no undesirable clinical sequels observed neither on any member of the experimental group nor on the medical personnel that participated in the experiment; additionally, in the absence of detrimental physiological effects, the relative safeness of the ingestion of ClO_2 and its metabolites was proved. The most relevant sample of successful application of ClO_2 is the one occurred in Bolivia, where the authorities passed the *Ley sobre la Producción, Uso y Distribución de Dióxido de Cloro (CDS)* (Law about the Production, Use and Distribution of Chlorine Dioxide (CDS)) and which was applied nationwide reducing in this way the mortality rate from 100 deceases at the beginning of September 2020 to only 6 in just two months[21].

6 Proposals

The utilization of aqueous solutions of ClO_2 for human consumption has been being promoted more enthusistically since the advent of COVID-19. Kály-Kullai et al.[20] propose considering the possibility of generating and putting to work effective public health protocols based on ClO_2, while Quevedo et al.[38] have found that the use of the same compund at a purity degree of 99% in dilution 1/2.5 inactivates the family of coronavirus in industrial plants. Likewise, the GHLC has developed a parameterized protocol[24] that has been a solid start basis for both scientists member of this organization as well as health-care professionals worldwide in their efforts to achieve a successful treatment against coronavirus. Hence, based on both the evidence generated by the scientific body and published in the literature and the field experience manifested by physicians who, independently, have consulted and redeemed patients infected with COVID-19 utilizing ClO_2, is that these proposals are put under consideration:

- To ask local government authorities for authorization to summon the best of the local health-care scientists in order to form a panel of experts who could analyze the scientific validity of the utilization of ClO_2 in both the preventive as well as the therapeutic treatment of viral diseases, among them, coronavirus. At this point, it is important to note, first, that ClO_2 does not generate immunity; also, the use of the protocol should be just another alternative to face coronavirus, alternative which should be available to those who voluntarily so wish.
- If this panel is formed and if it finds it so convenient:
  - Contact a GHLC representative to organize the collegiate use of ClO_2 in the treatment of an experimental group formed by local volunteers infected with coronavirus.
  - Keep a detailed journal and electronic registers of the procedures, doses, concentrations, physiological data (sex, age, weigth, current and chronic illnesses, possible adictions and others) of the subjects members of the experimental group so that protocols of preventive, therapeutic and post-therapeutic treatment could be optimized.
  - Extend the design of the protocols to administer it to persons who are, or have been, in constant with the infected subject.
  - Socialize the protocols among the local medical body, both in the public health centers as well as information open to the society.
  - Provide the health centers the chemical compound ClO_2, as well as the necessary equipment to apply the protocols.
  - Request the society its cooperation by means of observing minimal preventive measures to reduce the risk of infection, that is, the use of masks, wash hands with a neutral soap, take a bath after being in crowded places, avoid hand-shaking, etc., until sanitary authorities determine that herd inmunity has been achieved.
  - Publish the results in the literature.
  - Make emphasis before the society that the use of ClO_2 must be carried out ALWAYS UNDER THE SUPERVISION OF A DOCTOR EXPERIENCED IN THE USE OF THIS COMPOUND! and that self-diagnosis and automedication must be avoided since its incorrect use can even cause death.

7 Research topics

7.1 In progress

Nowadays, there is a wide diversity of research works related to the application of ClO_2, from which a few conducted by the *National Library of Medicine*, EEUU, as of January 26, 2021, are mentioned:

- Effects of extremely low-concentration gaseous chlorine dioxide against surface Escherichia coli, Pseudomonas aeruginosa and Acinetobacter baumannii in wet conditions on glass dishes. `https://pubmed.ncbi.nlm.nih.gov/32051032`.
- *In Vitro* and *In Vivo* Inhibitory Effects of Gaseous Chlorine Dioxide against *Fusarium oxysporum* f. sp. *batatas* Isolated from Stored Sweetpotato: Study II. `https://pubmed.ncbi.nlm.nih.gov/31632219`.

- The ability of two chlorine dioxide chemistries to inactivate human papillomavirus-contaminaded endocavitary ultrasound probes and nasendoscopes. `https://pubmed.ncbi.nlm.nih.gov/31919857`.
- Chlorine dioxide inhibits the replication of porcine reproductive and respiratory syndrome virus by blocking viral attachment. `https://pubmed.ncbi.nlm.nih.gov/30395996`.

7.2 Proposals

- Use of nanorobots to monitor the behavior of pH in carcinogenic tissues as a consequence of ClO_2-based treatments.
- Effect of pH on the molecular structure of ClO_2.
- Effect of pressure and temperture in the explosiveness of ClO_2.
- Optimization of the GHLC parameterized protocol using Taguchi techniques[44].

8 Conclusion

Based on a number of published research works conducted strictly under the rigor of the scientific method, it is uncontestable that chlorine dioxide has the appropriate physicochemical properties to fight microorganisms noxious to human health; additionaly, vast field experience has shown that, UNDER THE SUPERVISION OF AN EXPERIENCED PHYSICIAN!, the utilization of this compound under the GHLC parameterized protocol can help in both reducing the risk of infection as well as healing persons infected with COVID-19.

9 Addendum

The author declares not to have any conflict of interest in relation to the content of this document.

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