GENERAL DENTISTRY

Molecular iodine offers new hope to periodontal patients: How does it compare to chlorhexidine?

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Chlorhexidine gluconate (CHX) was first introduced into clinical practice in 1954.[1] In its more than 70 years of clinical use, it has become a standard of care in infection control, globally. CHX oral rinse has earned the American Dental Association's Seal of Acceptance and has been a valuable adjunct in the control of periodontal disease for decades. But has it outlived its usefulness? Let's compare the features and benefits of CHX to a current state-of-the-art antiseptic agent, molecular iodine (I2), that is currently being introduced into Canada so that you can answer that question.

Just because an antiseptic agent has earned prominence as a standard of care, doesn't mean that it will always retain that distinction. For example, during the 1930's and early 1940's, sulfa drugs were considered the standard of care as antibiotic agents. With the large-scale introduction of penicillin in 1945, sulfa was no longer considered the antibiotic of choice.[2] Consider your own practice today. When was the last time you prescribed sulfa for an infection?

So, how do CHX and I2 really compare in parameters that are important to our patients and to our practices? Let's first look at their relative antimicrobial efficacy.

CHX has excellent biocidal activity against periodontal bacteria, but I2 is considerably more effective. In Table 1, seven of the most commonly used professional periodontal rinses were compared for their biocidal efficacy against two key periodontal pathogens (Fusobacterium nucleatum and Prevotella intermedia). At 30 seconds exposure time, I2 was the only rinse found to be fully effective. It was 28 times more effective than CHX against Fusobacterium and 730 times more effective than CHX against Prevotella. It was also far more effective than every other rinse tested. This is no small feat, since all the testing was done in the presence of fresh, human whole saliva, which neutralizes most antiseptic rinses.[3]

We are not just concerned about periodontal bacteria. How effective are CHX and I2 against cariogenic bacteria? Table 2 shows the relative biocidal efficacy of CHX and I2 against Strep mutans, a principal caries-causing pathogen. Within 15 seconds, I2 completely destroyed all bacteria present with a 6+ log reduction. CHX achieved a 0.18 log reduction against Strep mutans in the same time frame. That 0.18 log reduction by CHX is the equivalent of starting with 1 million viable Strep mutans bacteria, exposing it to CHX for 15 seconds, and having 810,000 viable bacteria remain unscathed.[4]

Let's turn to viruses. How effective are CHX and I2 against important viruses? Table 3 helps to answer that question. Four different rinses were evaluated for their efficacy against SARS Co V-2. The testing was conducted at the Institute for Antiviral Research at Utah State University. Only one rinse was fully effective, a molecular iodine rinse. It was fully effective at just 30 seconds exposure time. None of the other rinses, including CHX were fully effective. Not at 30 seconds and not even when the exposure time was doubled to 60 seconds.[5]

Let's try another virus. Rhinovirus is a common upper respiratory virus responsible for most cases of viral pharyngitis. It is a difficult-to-kill non-enveloped virus. Table 4 compares the antiviral efficacy of CHX to I2 against Rhinovirus. Within 30 seconds, I2 completely destroys Rhinovirus. In that same time frame, CHX has no biocidal efficacy, at all.[6]

What about their effectiveness against fungi? Table 5 compares the relative efficacy of a 300 ppm molecular iodine solution to a solution consisting of 2% CHX and 70% isopropyl alcohol. Both the molecular iodine solution and the CHX/alcohol solution were tested against Aspergillus brasiliensis, one of the most resilient fungi known. The I2 solution completely inactivated the fungus within 15 minutes. The CHX/alcohol solution took one full hour to achieve the same result.[6]

What about safety? Which product is safer to use? Iodine is an essential nutrient required in the diets of humans to avoid iodine deficiency diseases.[7] That's why our salt is iodized. Iodizing salt is an inexpensive public health measure to help us avoid iodine deficiency diseases (including birth defects and mental retardation).[7]

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Not only does I2 have an excellent safety profile, but it is, perhaps, the most effective antimicrobial agent for human use as well as being amongst the safest to use. It can be used safely, each and every day by patients, literally for the rest of their lives.

CHX, unfortunately has serious health concerns. It is a potential carcinogen. Every bottle of CHX oral rinse sold in the U.S. is required by FDA to include a safety data sheet which states that it "may cause cancer" *(Fig. 1)*. It is categorized by FDA as a class 1A carcinogen, meaning that the evidence supporting that classification is based on actual human data.[8]

FDA has also issued a safety warning for CHX in response to a rising number of allergic reactions.[9] These reactions can be so severe that life threatening anaphylactic shock from the use of CHX has been reported on multiple occasions.[10] CHX also allows bacterial resistance to develop. The medical literature is replete with references to bacterial resistance development associated with CHX use.[11] The rapid increase in patients becoming resistant to antimicrobial agents has become alarming. In a study conducted at Temple University Dental School, it has been shown that within the 20-year time span ending in 2020, 16 times as many periodontal patients became resistant to Clindamycin at the end of the study as compared to the beginning and 28 times as many patients became resistant to Amoxicillin.[12]

Iodine does not cause microbial resistance.[13] Nowhere in the medical literature is there any evidence of microbial resistance development to iodine. Because of safety concerns CHX is only indicated for short-term, episodic use, not to exceed two weeks.[14] Because CHX is not effective against certain resilient bacteria, FDA has also issued multiple recalls for CHX because of microbial contamination by bacteria living within the CHX rinse bottles.[15,16]

Antimicrobial efficacy and product safety are critically important attributes of our antiseptic agents, but there are other important product characteristics that can spell the difference between treatment failure and treatment success. Table 7 shows important product characteristics for

Table 1

	Log reduction at 30 seconds	
Antiseptic rinse	***Fusobacterium nucleatum***	***Prevotella intermedia***
ioRinse Ultra	**6.0 -** complete inactivation	**6.0 -** complete inactivation
Chlorhexidine gluconate 0.12%	**4.8 -** 28x less effective	**3.3 -** 730x less effective
Cetylpyridinium chloride 0.07%	**0.2 -** 820.000x less effective	**5.3 -** 7x less effective
Chlorine dioxide	**0.71 -** 361.000x less effective	**3.9 -** 190x less effective
Povidone iodine 10%	**1.8 -** 28.000x less effective	**1.3 -** 73.000x less effective
Hydrogen peroxide	**0.4 -** 640.000x less effective	**0.52 -** 532.000x less effective
Stabilized chlorine dioxide	**0.04 -** 964.000x less effective	**0 -** no biocidal activity

Note: All testing conducted in the presence of fresh, human, whole saliva at Prime Analytics Laboratory, Concord, California

Table 2

Microorganism	**Molecular Iodine (Iz)**			**Chlorhexidine Gluconate**		
	Strength	**Log Reduction**	**Time**	**Strength**	**Log Reduction**	**Time**
Strep mutans	100 ppm	6.49 complete inactivation	15 sec.	0.12%	0.19	15 sec.

Source: BioScience Laboratories, Bozeman, Montana

Table 3

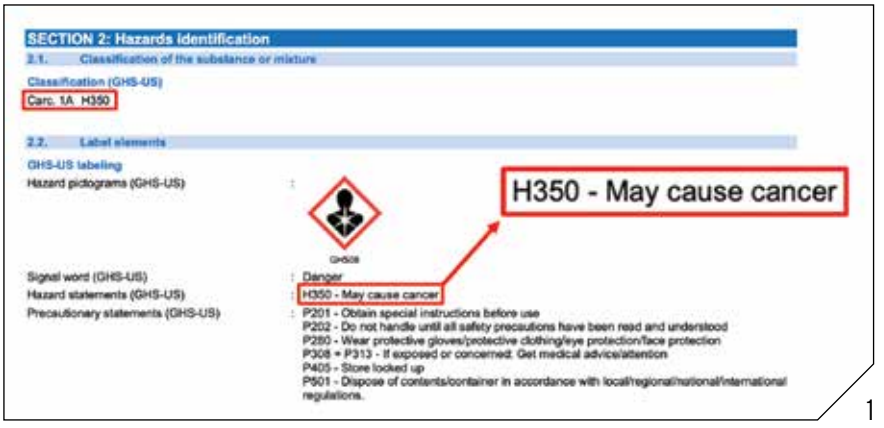
Oral Rinse	**Log Reduction**		**Observed Cytotoxicity**
	30 Seconds	**60 Seconds**	
1.5% hydrogen peroxide	<1.0	<1.0	1/10,1/100, 1/1000 dilutions
0.2% povidone iodine	2.0	3.0	none
0.12% chlorhexidine gluconate	<1.0	1.0	1/10,1/100 dilutions
Molecular iodine formula 100-S	>3.6 Complete inactivation	>3.6 Complete inactivation	none

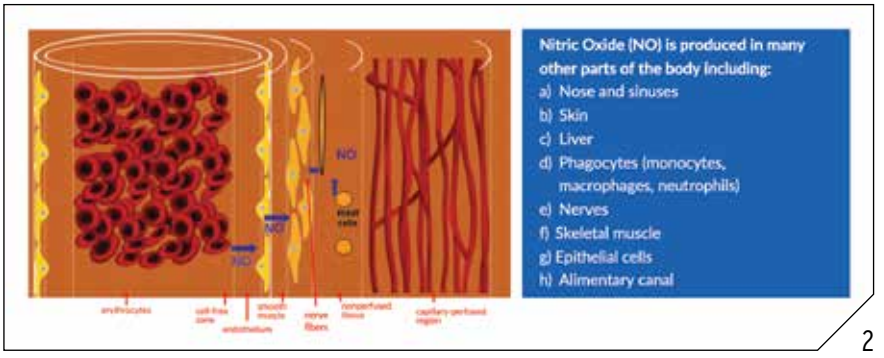
Source: Utah State University, Institute for Antiviral Research; August 3, 2020

Table 4

Microorganism	**Molecular Iodine (I_2)**			**Chlorhexidine Gluconate**		
	Strength	**Log Reduction**	**Time**	**Strength**	**Log Reduction**	**Time**
Rhinovirus	25 ppm	4.0 complete inactivation	30 sec.	0.12%	0.0	30 sec.

Source: BioScience Laboratories, Bozeman, Montana





1. SDS Chlorhexidine Gluconate 0.12. **2.** Source: Johns Hopkins School of Medicine, University of Virginia Medical School Nov, 2008

Table 5

Antiseptic Agent	Time Required for Complete Inactivation (4.0+ log reduction)
CHX 2.0% (17x stronger than 0.12% CHX oral rinse) + Isopropyl Alcohol 70%	60 minutes
Molecular Iodine (300 ppm)	15 minutes

Sources: 1. Yoshida Pharmaceutical Company. In-house testing, May 2017. 2. Care Fusion U.K. ChloraPrep Summary of Product Characteristics. January, 2016

Table 6

Antibiotic	Change in number of resistant perio patients Year 2000 >> Year 2020
Clindamycin	16x greater
Amoxicillin	28x greater

Source: Emergence of Antibiotic-Resistant Porphormonas gingivalis in United States Periodontal Patients. Rams, T. Antibiotics 2023 Nov 1, 12(11) 1584

both CHX and I2 oral rinses. CHX interferes with both soft tissue repair and bony regrowth because of its inhibitory activity against fibroblasts and osteoblasts.[17] Periodontal pocket depth reduction and clinical attachment gain are impeded by this inhibitory activity. Unlike povidone iodine and chlorhexidine gluconate, molecular iodine rinses do not stain.[18] It has been shown that CHX degrades the biocompatibility of titanium surfaces. It is therefore contraindicated for use with titanium implants because implants that are no longer biocompatible, cause local tissue reaction leading to peri-implant mucositis and also peri-implantitis.[19]

A molecular iodine oral rinse checks all the boxes in being as nearly perfect as an antiseptic rinse can be. Because molecular iodine has such broad-spectrum activity, wouldn't it be expected to destroy nitric oxide-producing bacteria in the mouth, as well? Wouldn't a lower nitric oxide level then lead to negative changes in vaso-activity and ultimately heart disease? The answer may surprise you.

Yes, molecular iodine will destroy nitric oxide-producing bacteria along with pathogenic bacteria, but the limited production of nitric oxide produced in the mouth has only a negligible effect, if any, on vaso-activity. A joint study by John Hopkins School of Medicine and the University of Virginia Medical School demonstrate conclusively that the key production of nitric oxide involved in vaso-regulation is located in and around the blood vessels themselves, not in the mouth. They also point out that nitric oxide is produced almost everywhere in the body (skin, skeletal muscle, nose and sinuses, liver, blood cells, epithelial cells, nerves and all throughout the alimentary canal) *(Fig. 2)*.

What about dysbiosis of the oral microbiome? Wouldn't inactivation of commensal bacteria by a powerful antiseptic rinse lead to dysbiosis? The mouth is never sterilized with the use of an antiseptic rinse. Residual, viable microbes, with the help of microbes from the nose, the throat, and the air we breathe, rapidly repopulate. It is postulated that repopulation of gram-positive, aerobic bacteria occurs more quickly and completely than does repopulation of anaerobic, patho-

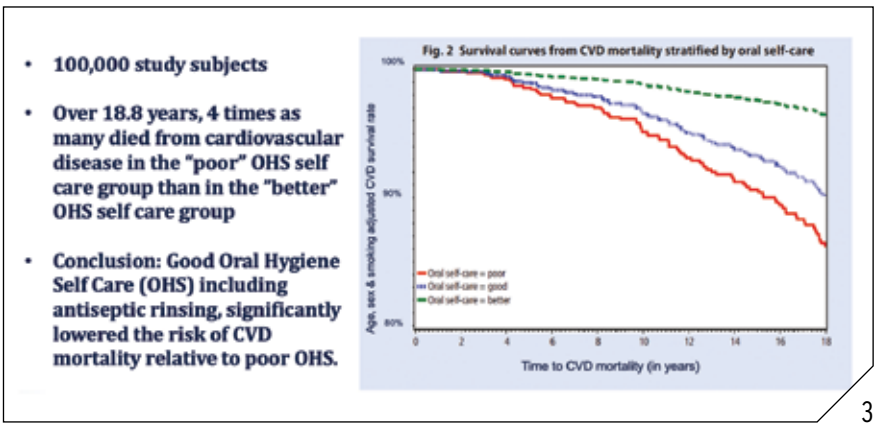
genic bacteria.[24] It is the rapid repopulation of these aerobic bacteria that crowds out the anaerobes, establishing a new microbiome favoring commensal bacteria.

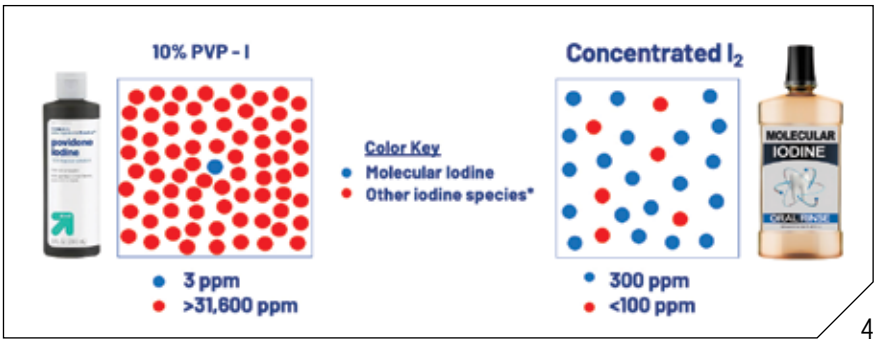
We should also not lose sight of the fact that controlling periodontal disease is critical in helping to control heart disease. Periodontal disease has reached epidemic proportions, and the most effective antiseptic agents are required to help us control periodontal disease.[24]

In a recent landmark study reported in the British Dental Journal, 100,000 patients were stratified into 3 groups depending on the level of their daily, at-home oral hygiene (poor at-home oral hygiene, moderate at-home oral hygiene and best at-home oral hygiene). These patients were followed for almost 19 years, tracking the number of deaths attributable to cardiovascular disease that occurred in each group. The most significant finding was that 4 times as many patients died from cardiovascular disease in the poor periodontal health group than did in the best periodontal health group.

Is molecular iodine a newly discovered molecule? Oddly, molecular iodine or I2 has been around as long as iodine has been around. Early Chinese physicians provided the first recorded evidence of therapeutic benefit of using iodine-rich substances more than 5,600 years ago. They formulated pastes of ground up seaweed and sea urchins, applying these pastes to the necks of patients who had goiters (enlarged thyroid glands)20. Although they were successful in shrinking the size of many of these goiters, they had no idea that the active agent in these pastes was iodine. It wasn't until 1814 that the French researcher, Courtois identified iodine as an element.[21]

Figure 4 shows two schematic diagrams. The schematic on the left represents 10% povidone iodine. It contains approximately 31,600 ppm of total iodine. Of all the different species of iodine in povidone iodine, only one species is biocidal and actually kills germs. That species is molecular iodine (I2)[6] and it is only present in povidone iodine at trace levels (2-3 ppm).[6] As almost unimaginable as it may be, those 2-3 ppm of I2 account for all of povidone iodine's germicidal activity. The schematic





3. Mouthwash Usage and Cardiovascular Mortality During 18.8 years of Follow-up. Source: British Dental Journal Feb, 2023 **4.** Source: Moskowitz, H. (2024) Oral Rinses: What's Safe? What's Effective? Dental CE Academy. https://www.dentalceacademy.com/iotech-international-on-demand-webi

Table 7

Product Characteristics of CHX and I Oral Rinses		
Characteristic	**CHX Oral Rinse**	**I_2 Oral Rinse**
FDA safety warning issued	Yes	No
FDA recalls for microbial contamination	Yes	No
Inhibits fibroblast proliferation	Yes	No
Inhibits osteoblastic activity	Yes	No
Stained teeth and tongue	Yes	No
Promotes dental calculus buildup	Yes	No
Alters taste	Yes	No
Use limited to short term only	Yes	No
Allows microbial resistance development	Yes	No
Compromises implant biocompatibility	Yes	No

Source: Antimicrobial Agents Used in the Treatment of Peri-implantitis Alter the Physicochemistry and Compatibility of Titanium Surfaces. Journal of Periodontology DOI 10.1902/jop.2016.150684

on the right side of Figure 2 shows a high-level molecular iodine solution containing 300 ppm I2. Only trace levels of other iodine species are present in this high-level iodine solution, so it does not stain.[18]

For decades, researchers have tried unsuccessfully to develop high level molecular iodine solutions while suppressing other iodine species which are toxic and staining. I2 is unstable and quickly morphs into other forms of iodine which are not biocidal.[22] So even if it was possible to add I2 to povidone iodine, it wouldn't stay as I2 but would rapidly change into other non-biocidal species of iodine.

In 2016, after 3 years of painstaking research focused on this very problem, Iotech International, a Florida-based medical technology company, developed the breakthrough technology that has ushered in a new generation of stable, high level molecular iodine oral care products which have been patented globally and have a useful shelf life of 2 years.[23]

These products are already successfully being used in thousands of dental offices in the U.S. and are now being introduced into Canada through Henry Schein-Canada. You should now be able to answer the question, "How does molecular iodine compare to chlorhexidine?" Perhaps a more important question to ask yourself is "If molecular iodine oral rinse is available, why am I still using chlorhexidine?". OH

Oral Health welcomes this original article.

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