Effects of Zinc on Oral Bacteria and Volatile Sulfur Compound (VSC) in Oral Cavity

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Zinc compounds have been used in various fields - cosmetics, medicine, and dentistry - because of its effective functions to human tissues or organs. Especially, it is well known that zinc has many biologic effects in oral cavity. Zinc ion can affect various oral microorganisms, resulting in reduction of oral bacteria, dental plaque, and dental caries. Also, zinc ion has an ability to reduce amounts of oral anaerobic bacteria and oral VSC and can reduce oral malodor. The author summarized the characteristics and toxicity of zinc, several forms of zinc compounds applied in human tissues, and reviewed biologic effects of Zinc in oral cavity (anti-bacterial effects, anti-plaque effects, anti-caries effects, and anti-VSC effects of zinc).

Because of many advantages of zinc in oral cavity, it can be concluded that application of zinc compound to various oral diseases will be extended and activated, and promising.

Key words: Zinc, Anti-bacterial effect, Anti-plaque effect, Anti-caries effect, Volatile sulfur compound, Oral malodor

I. INTRODUCTION

Zinc is an essential trace metal in human metabolism and it has been used as therapeutics in cosmetics, medicine, and dentistry, because of its various medical functions to human body and less toxicity than other metals.

Before reviewing biologic effects of zinc ions on oral microorganisms and volatile sulfur compound (VSC) in oral cavity, in this section, the author will summarize the characteristics of zinc, toxicity of zinc, and several forms of zinc compounds applied in human tissues.

1. Characteristics of Zinc

Zinc is a bluish white metal showing a crystalline fracture. It is available in the form of ingots, sheets, sticks, shot, and powder. It is harder than silver but softer than copper. It has a specific gravity of 7.14. It melts at 419°C, and boils at 907°C. Zinc is stable in dry air, but in moist air it becomes covered with a coating of basic zinc carbonate. When pure, it is very slowly acted upon by diluted sulfuric or hydrochloric aids and the presence of a small amount of another metal increases the action of these acids. It is readily soluble in solutions of the fixed alkali hydroxides with the evolution of hydrogen. It is slowly dissolved by ammonia water. Zinc is divalent and readily combines with oxygen and the halogens. It also unites with phosphorus to form zinc.
phosphide. It reacts with most acids with the liberation of hydrogen. All of zinc salts, with the exception of the sulfide, are soluble in solutions of the fixed alkali hydroxides, and all but the ferrocyanide and the sulfide are soluble in ammonia water.\(^1\)\(^-\)\(^3\)

The name of ‘zinc’ is derived from ‘zinken’, a word used by Paracelsus who regarded the element as a semi–metal. Although the alloy of the metal zinc and copper called ‘brass’ was known to the Romans, the metal zinc dose not appear to have been separated and described until the sixteenth centuries. Its identity was a mystery for several centuries. Paracelsus thought it was a form of copper, other thought it was altered mercury, tin, or bismuth.\(^3\)

2. Toxicity of Zinc

Zinc has less toxicity than other metals (e.g., lead, arsenic, cadmium, antimony). So, rare fatalities have been reported. Gastroenteritis resulting from zinc toxicity most commonly presents after ingestion of acid foods from galvanized containers. Especially, zinc chloride is a caustic that causes irritation of the gastrointestinal tract, pancreas, kidney, and lungs.\(^3\)

It is known that the chloride salt of zinc is the most toxic form and there was a report that indigestion of 1 g of zinc chloride per kilogram by a child resulted in minimal systemic effects. Its powerful emetic properties (e.g., the adult emetic dose is 225–450 mg) limit its toxicity.\(^2\)

Inhalation of zinc oxide is the most common cause of metal fume fever and inhalation of fumes may cause various complication–sweet taste, throat dryness, cough, weakness, generalized aching, chills, fever, nausea, vomiting. Especially, zinc chloride fumes have caused injury to mucous membranes and skin irritation.\(^1\)

Zinc is a cofactor for biologically important enzymes. Excessive zinc intake interferes with copper absorption, impairs lymphocyte and neutrophil function, and appears to reduce serum levels of high-density lipoprotein cholesterol while causing a transient elevation in serum low-density lipoprotein cholesterol.\(^2\)

3. Zinc compounds for cosmetic & medical use

In dermatology, zinc has been used for wound healing and treatment of skin disease. Its mechanisms are not clear, but zinc is thought to stabilize a lot of tissue proteins in wounds and facilitate the recovery from the loss of human tissue. Zinc is known to have an antiseptic function, and its mode of action to the bacteria will be discussed later in this article.

There are several forms of zinc compounds which is commonly used in cosmetics and medicine, including zinc acetate, zinc carbonate, zinc chloride, zinc citrate, and zinc iodide, zinc oxide, zinc sulfate.\(^3\)

First, zinc acetate is a water–soluble compound used as antiseptics or topical protective, and has been used as emetics. In ophthalmology, 0.1–1.0% zinc acetate eye wash solution is used for the treatment of conjunctivitis.

Second, zinc carbonate is used as astringent, topical antiseptic and also used in rations to prevent Zn deficiency disease.

Third, zinc chloride is odorless, water–soluble agent and its color is white. It has antiseptic and astringent actions and is used as deodorant, disinfectant, and embalming material.

Fourth, zinc citrate is commonly used in toothpastes and mouthwashes.

Fifth, zinc iodide is white, odorless, hygroscopic, and granular powder. It has sharp and saline tastes. It is applied to topical antiseptics and astringents. Its diluted solution is used as astringent injection in gonorrhea.

Sixth, zinc oxide is white or yellowish–white odorless powder and has mild astringent and antiseptic actions. Commonly, it is used for the treatment of skin disease and infections.

Seventh, zinc sulfate is water–soluble salts of zinc commonly employed for their antiseptic and astringent action. Generally, it is used as ophthalmic astringent and may be applied to the skin as a 4%
solution in the treatment of acne, lupus erythematosus, and impertigo. For skin application, it is commonly employed in the form of white lotion.

II BIOLOGIC EFFECTS OF ZINC IN ORAL CAVITY

It is reported that zinc has many biologic effects in oral cavity. Zinc causes various changes of oral microorganisms—anti-bacterial effects, anti-plaque effects, and anti-caries effects. Also, zinc has anti-VSC effects and can reduce oral malodor.

Many years ago, researchers have suggested various theories about effects of zinc on oral microorganisms. The most supported mechanisms are as follows.

① Oxidation of thiol groups of oral bacterial enzymes

In 1980, Oppermann and Rolla\(^4\) compared the effect of AlCl\(_3\), FeCl\(_3\), MgCl\(_2\), SnF\(_2\), ZnCl\(_2\), and chlorhexidine on the acidogenicity of dental plaque in vivo. They found the cations themselves reduced the acid production of plaque and gave one possible mechanism that oxidation, by certain metals, of essential thiol groups of bacterial enzymes involved in the inhibition of bacterial metabolism of glycolysis. After the study, they proved this theory is true by another successive experiment.\(^5\)

② Displacement of Mg ion essential for enzymatic processes

Zinc may displace cations essential for enzymatic processes of the bacteria. The magnesium ion is known to be required in a number of enzymatic reactions responsible for the transport of carbohydrates into the bacterial cell. So, one aspect of the inhibiting effect of zinc ion can be due to displacement of Mg in bacteria.\(^6\)

③ Non-specific reaction between zinc ion and negative-charged proteins

The antimicrobial action of zinc may also involve a nonspecific interaction with negatively charged proteins.\(^7\)

④ Interference with bacterial protein profiles

Jones and Purdell–Lewis(1988) suggested that the antimicrobial activity of zinc is related to direct changes in the structure of bacterial cell proteins. Zinc may act indirectly by inhibiting protease induced adhesion.\(^8\)

⑤ Change of bacterial surface potential and inhibition of bacterial adhesion to teeth

Gedalia \(\text{et al.}\)\(^10\) performed the experiments to assess the inhibitory effect of ZnCl\(_2\) mouth rinse on dental plaque accumulation in humans and the effect on the concentration of zinc in the surface enamel of the teeth. The result was that plaque indices were reduced during the initial and post-experimental period of 15 days. As the mechanisms of action of zinc, they suggested that binding of zinc to the surface of oral bacteria can alter their surface potential and this may affect bacterial adhesion to teeth.

⑥ Change of nutrient transport into bacteria

In 1983, Harrap and Saxton observed that solutions of 17–19 mM zinc as the citrate or phenolsulphonate salt, gave about 30% reduction in the extension of plaque along the gingival margin in vivo over 16 hours. They thought zinc can reduce bacterial growth, possibly by affecting nutrient transport into bacteria.\(^11\) First, zinc ions may adsorb on the bacterial cell wall and these absorbed zinc ions may be transported into the bacterial cell or remain at cell membrane where affects on glucose transport system.\(^12,13\)

It has been suggested that glucose uptake system by \(S.\) mutans occurs by two different mechanisms: one, via the glucose phosphotransferase transport system (PTS), the other, driven by the energy of proton electro–chemical gradients (PMF mechanism).\(^14\) Zinc preferentially inhibited the PTS system and zinc may reduce glucose uptake by inhibition of enzyme I in the PTS. The PMF mechanism is especially important at low pH and account for glucose uptake by \(S.\) mutans at low plaque pH.\(^15\) (Fig. 1)
Zinc has also been proposed to inhibit glycolysis through inhibition of sulphhydryl enzymes, aldolase and glyceraldehydes dehydrogenase.15-17) (Fig. 2)

1. Anti-bacterial effects of zinc

There are a lot of researches about antimicrobial properties of zinc compounds. Most of the proposed mechanisms, explaining in biologic effects of zinc on oral microorganisms, may be responsible for anti-bacterial effects of it: inhibition of oxidation of essential thiol groups of bacterial enzymes, displacement of Mg ion essential for enzymatic processes, non-specific reaction to (-) charged proteins in bacteria, inhibition of protein profile in bacteria, and reduction of bacterial growth by reducing metabolic activity. But definite mechanisms of metal ion such as zinc and tin are not established clearly.18)

2. Anti-plaque effects of zinc

Anti-plaque effects of zinc ion were first observed by Hanke in 1940.

Inhibition of the formation and metabolism of dental plaque by zinc salts has been well documented.19-22) The mechanisms remain unclear, but studies suggest that free zinc ions are responsible22,23) and that the reduction of acidogenicity is correlated with adsorption of zinc on the bacterial cell wall20 and affecting nutrient transport into bacteria.11) Other proposed mechanism supporting anti-plaque effect of zinc is the change of bacterial surface potential and inhibition of bacterial adhesion to teeth.10)

Clinical anti-plaque activity of zinc appears to vary widely. Saxton et al.23) suggested a dose-dependent, plaque-inhibiting effect of dentifrices containing zinc citrate and triclosan. Reduction of plaque formation by toothpaste containing 0.5% zinc citrate has been reported to range from 024) to 42%.25) Similarly, the zinc concentration responsible for halving the plaque pH drop following glucose exposure in vivo ranges from 526) to 100 mM.19) Such variation may be due to factors other than concentration26) : a difference in zinc salts applied, methods of application, and different methods used to score plaque development or measure acidogenicity. Moreover, the plaque-inhibiting effect of zinc may vary between individuals because heavy plaque formers benefited more from zinc compounds than subjects with low or moderate plaque.23)
3. **Anti-caries effects of zinc**

An inverse relationship between the presence of certain metals in plaque and caries experience was reported. So, it can be suggested inhibition of bacterial acid metabolism by metal ions contribute to a reduction of dental caries.\(^5\)

Several studies have shown that a variety of metal ions inhibit the acid production of plaque bacteria in the presence of sucrose.\(^5\) However, few of theories about the mechanisms how zinc can reduce acidogenicity of oral bacteria have been suggested until now. In 1991, Watson *et al.*\(^12\) reported that zinc ions were strongly inhibitory to acid production during glucose metabolism by *S. mutans* and this inhibition was closely associated with adsorption of zinc to the bacterial cells. Their results implicates dose-related inhibition of Zn ion during glucose metabolism by *S. mutans*.\(^22\) Also, certain bacterial enzyme involved in the transport and metabolism of carbohydrates contain thiol groups. Some metal ions, such as silver, tin, and zinc, were known to exert inhibitory effect on bacterial acid production by oxidation of thiol groups of bacterial enzymes.\(^5\)

Other researchers suggested that zinc ions change the surface potential and affinity of oral bacteria to tooth surface. So acidogenicity in the dental plaque is lowered. Moreover, the displacement of Mg ion in bacterial enzyme by zinc ion affects the acid production by oral bacteria.

Because of its potential importance in caries prevention, the studies about different effects of zinc on glycolysis among various oral bacteria have often been studied in *vitro*. The effect of 6.1mM Zn on the some of oral bacteria suggested that *S. mutans* is the most sensitive to zinc.\(^27\) As another study monitoring the effect of zinc reported that streptococci had the highest acidogenesis rates in both pH-stat and pH-fall experiments, it seems likely that inhibition of acid production with these organisms would be of value in moderating caries than the inhibition of less acidogenic organisms such as *A. naeslundii*.\(^19\)

### III. **ANTI-VSC EFFECTS OF ZINC**

It is generally accepted that volatile sulfur compounds (VSC)–hydrogen sulfide, methyl mercaptan, and dimethyl sulfide constitute the major component of oral malodor originating from the oral cavity.\(^26,29\)

It is well established that aqueous solutions of some metal ion, such as Cu, Sn, Zn have a major effect on VSC, reducing or eliminating the unpleasant odor.

The mechanism of anti-VSC effect is assumed that metal ions, due to their affinity for sulfur, oxidize thiol groups in the sulfur-containing precursors of VSCs and convert them into non-volatile substances. The anti-VSC effects are probably also related to the antibacterial properties of the metal ions.\(^30\)

Several metal ions have higher affinity for sulfur and greater antimicrobial activity than zinc. But, the VSC-inhibiting effects are not positively correlated to sulfur affinity. Properties other than sulfur affinity are probably important for the clinical effect of metal ions against VSC production. It is well known that zinc ions have high affinity for carboxyl and phosphate groups, which presumably are exposed on the surface of oral tissues, on bacteria, and in salivary macromolecules. This binding probably involves displacement of counterions (Ca ion) into zinc. Other metal ions in the mouth may rapidly become oxidized and thus lose their affinity for sulfur. It may be speculated that a gradual subsequent release of the absorbed zinc by competing Ca ions from newly secreted saliva may provide a mechanism resulting in a long-term retention of Zn.\(^30\) And, zinc is less reactive than Cu and Sn, so zinc can exist much longer in oral cavity. Besides, zinc participates in a wide range of regulatory mechanisms and may well be involved in the enzymatically regulated process by which the sulfur-containing amino acids are metabolized to yield VSCs. Furthermore, smaller zinc ion could also be significant by affecting steric relationships.\(^30\)

Although Cu and Sn ion may have the superior
effects, these metal ions have the potential to discolor the teeth, either as a result of sulfide formation on the teeth after extended periods of use or due to the precipitation of dietary chromogens.\(^3\) On the other hand, zinc appears to be the most promising efficient, with a favorable cost–benefit relationship, and staining of the teeth by zinc ion is rare. Also, Zinc has low toxicity to oral tissue, so prolonged application of zinc solution to oral cavity is relatively safe. The prolonged use of a dentifrice containing 0.5% zinc citrate did not affect the salivary concentrations of lysozyme, lactoferrin, immunoglobulin A, total protein, nor reduce the activity of salivary peroxidase. In other words, 0.5% zinc citrate dentifrice does not inhibit the non-specific salivary antimicrobial system.\(^32\) Therefore, zinc has been the most popular metal ion for use in commercial preparations aimed at improving the oral malodor, even if its effect is moderate.\(^3\)

Various researches that monitored reduction in oral malodor using the zinc solutions are shown in Table 1. Since Tonzetich and Ng first used zinc solution to study anti-VSC effects,\(^33\) Schmidt and Tarbet\(^34\) reported that a mouse rinse containing zinc chloride was remarkably more effective than a saline rinse or no treatment in reducing the levels of both VSC and organoleptic score for a 3-hour duration. Recently, Halita, a mouthrinse containing 0.05% chlorhexidine, 0.05% Cetylpyridinium chloride, and 0.14% zinc lactate has been shown to be even more efficient than a 0.2% chlorhexidine formulation in reducing the VSC levels and organoleptic ratings.\(^35\) This special effect of Halita may be due to the VSC conversion ability of zinc, besides its antimicrobial action.\(^36\)

As the anti-VSC effect of zinc is dependent on the presence of zinc as free ions, it appears likely that zinc salts with low stability constants (that is, those which provide an abundance of free zinc ions in aqueous solutions) would be the preferable source of zinc in formulations designed to inhibit oral VSC production. Of the different zinc sources, zinc acetate and zinc gluconate provide abundant amounts of free zinc ions, whereas zinc citrate and amino acid-chelated zinc provide extremely low free zinc ions. But, some studies reported that zinc lozenge with the highest stability constant was as

<table>
<thead>
<tr>
<th>Agent</th>
<th>vehicle</th>
<th>follow-up</th>
<th>outcome</th>
<th>comment</th>
<th>study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zn chloride (Lavoris)</td>
<td>Mouthrinse</td>
<td>2 hr.</td>
<td>Significant decrease in organoleptic &amp; VSC</td>
<td>Saline &amp; no Tx. controls</td>
<td>Schmidt &amp; Tarbet (34)</td>
</tr>
<tr>
<td>0.23% Zn-citrate &amp; 0.3% triclosan</td>
<td>Dentifrice</td>
<td>3 hr.</td>
<td>22% reduction in VSC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.23% Zn-citrate &amp; 0.3% triclosan</td>
<td>Dentifrice</td>
<td>21 days</td>
<td>35% reduction in VSC</td>
<td>Mouthrinse better than dentifrice</td>
<td>Raven et al. (38)</td>
</tr>
<tr>
<td>0.84% Zn-citrate &amp; 0.15% triclosan</td>
<td>Mouthrinse</td>
<td>21 days</td>
<td>66-83% reduction in VSC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zn chloride (Lavoris)</td>
<td>Mouthrinse</td>
<td>3 hr.</td>
<td>80% reduction in VSC</td>
<td></td>
<td>Tonzetich &amp; Ng (33)</td>
</tr>
<tr>
<td>Zn acetate (2mg)</td>
<td>Chewing gum</td>
<td></td>
<td>45% reduction in VSC</td>
<td></td>
<td>Waler (29)</td>
</tr>
<tr>
<td>0.02% ZnCl2</td>
<td>Mouthrinse</td>
<td>3 hr.</td>
<td>24% reduction in VSC</td>
<td>Significant better than CPC</td>
<td>Niles &amp; Gaffar (39)</td>
</tr>
</tbody>
</table>
effective as those with very low stability constants. The anti-VSC effect was thus not related to this constant.\textsuperscript{40,41} It appears that higher concentrations of much stronger competing ligands must be available in the oral cavity, causing a transfer of zinc ions from the original complexes to new, stronger ligands.\textsuperscript{40,41} An \textit{in vitro} experiment indicated that the sulfide ion may be such a strong ligand.\textsuperscript{40} And recent study\textsuperscript{42} monitoring insoluble zinc, cupric and tin pyrophosphates, supported this hypothesis that sulfide ions are obviously very strong ligands for these metal ions.

To apply some of zinc solutions to oral cavity, they must have favorable taste. Therefore, organic zinc salts is commonly formulated because of its less metallic taste.\textsuperscript{29} Generally, Zinc at 1% concentration had a somewhat unpleasant taste, whereas the lower concentration was found acceptable.\textsuperscript{43}

Many researches suggested various clinically effective concentration of zinc for reducing oral VSCs. If clinician focuses on the anti-bacterial, anti-plaque, and anti-caries effects of zinc, it is thought that concentration of free zinc ion is most important factor to determine clinical effects of zinc. Because, these effects is increased as the dose of free zinc ions become increased. However, in case of anti-VSC effect, another factor must be considered. Besides the dose-related effect, presence of strong ligands for metal ion must be considered. And it is reported that repeated application of lower concentration of zinc is more important, than irregular application of higher concentration of zinc solution.

It is controversial if zinc mouthrinse is more effective that zinc-containing toothpaste in reducing oral VSCs. But, if teeth, gingival, as well as tongue are all completely cleansed by proper tooth brushing, it is thought that zinc-containing toothpaste is as effective as zinc mouthwash with higher concentration of zinc ions. For repeated oral rinsing procedure after tooth brushing with zinc-containing toothpaste may weaken the effect of zinc ion, limited rinsing after brushing may be recommended.

Mouthrinse is often used on an irregular base, whereas dentifrice is commonly used on a daily basis, so individuals who are not ready to use gargling solutions, may prefer toothpastes to mouthrinses.

\section*{IV CONCLUSIONS}

Zinc compounds have been used in cosmetics, medicine, and dentistry because of its various medical functions to human body. Especially, it has been reported that zinc has many biologic effects in oral cavity. Zinc ion can affect various oral microorganisms resulting in reduction of amounts of oral bacteria, dental plaque, and dental caries. Also, zinc ion has an ability to reduce amounts of oral VSC and can reduce oral malodor. Zinc has less toxicity than other metals, and causes rare teeth discoloration. Moreover, it is cost–benefit, so it can be applied to oral infection, dental caries, periodontal disease, and oral malodor, as preventive agents or long-term therapeutics. Because of many advantages of zinc in oral cavity, it can be concluded that application of zinc compound to various oral diseases will increase.

\section*{REFERENCES}

구강내 세균과 휘발성 황화합물에 대한 아연의 영향

강릉대학교 치과대학 구강내과학전공학교실
김영준

아연 화합물은 의학적 효용이 뛰어나서 예전부터 화장품, 의약품 및 치과용 제제 등으로 널리 사용되어 왔다. 특히, 아연의 구강내 생물학적 작용에 대해서는 널리 알려져 있는데, 아연은 구강내 미생물에 다양한 기전으로 영향을 가해서 항균 작용, 항치태 작용, 항우식 작용을 갖게 된다. 또한, 아연은 구취를 유발하는 구강내 혐기성 세균과 휘발성 황화합물에 영향을 주어서 구취 치료제로서도 널리 예용되고 있다.

이에 저자는 아연의 개발적인 물성과 독성 및 상용되고 있는 아연 제제들을 요약하여 제시한 후, 구강내 세균과 휘발성 황화합물에 대한 아연의 생물학적 영향에 대하여 항균 효과, 항치태 효과, 항우식 효과 및 구취감소 효과 등으로 나누어 고찰해보았다.

아연은 다른 금속에 비하여 독성이 적고 치아 착색을 거의 유발하지 않으며, 가격 또한 저렴하여 구강내 감염, 치아우식증, 치주질환 및 구취 등의 예방 및 치료제로서 많은 장점을 지니고 있다. 향후 이러한 장점을 바탕으로, 치과 임상에서의 아연제제의 적용은 증가할 것으로 사료되며, 이에 대한 전망은 밝다고 할 수 있다.

주제어 : 아연, 항균 효과, 항치태 효과, 항우식 효과, 휘발성 황화합물, 구취