

Zinc Lozenges - a Cure for Common Colds?

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Common cold is the most frequent illness managed in the general practice. Colds afflict most adults 2-4 times a year and children 4-8 times a year, and the resulting loss of work time and school time has enormous economic bearings. Each year American women miss more than 13 million days of work due to the common cold and more than 33 million days due to influenza. It has been estimated that in the US over \$2 billion dollars are spent annually on over-the-counter medications for colds. More than 200 viruses can cause common colds in adults, but rhinoviruses (RV) are by far the most common culprit¹. Rhinoviruses account for about 40-50% of cold infections and are spread chiefly by aerosols generated by coughing, sneezing, and nose blowing. Over 100 RV serotypes have been identified, but most of these attach to a single cell receptor (ICAM-1) by a single binding site on virus²⁻³. After the HRV enters the airway, it docks on epithelial cells through ICAM-1 on apical side and upregulates expression of ICAM-1. High levels of ICAM-1 attract leukocytes to migrate through endothelial cell layer and attach to epithelial cells on basolateral side². Both the virus and the leukocytes use ICAM-1 to adhere to the surface of lung epithelial cells⁴. When leukocytes attach to epithelial cells, they degranulate the cell and induce inflammatory responses seen in common colds. Obstacle to developing effective treatments for the common cold is that viral replication in the upper respiratory tract peaks at the start of symptoms and thus, one key element is the start time of treatment. Different formulations of zinc have been evaluated as cold remedy since the publication of reports regarding zinc's antiviral activity. The use of these lozenges was first introduced in the early 1980s, but after reports questioning their efficacy were published, the use of zinc lozenges diminished. However, results from clinical trial by Mossad⁵ renewed the popularity of zinc lozenges for the treatment of common colds.

Role of Zinc in Immune Functions

Zinc is one of the elements required for normal functioning of cells and serves primarily as co-factor, especially for enzymes involved in DNA replication and transcription: thus it plays a vital role in growth and tissue maintenance⁶. The normal serum levels of zinc are - 0.015 MM Zn++ and the recommended dietary allowance (RDA) for zinc is -15 mg/day. Zinc levels in blood are controlled by homeostatic mechanisms and any excess is quickly removed from the circulation. Zinc deficiency leads to growth failure, dermatological manifestations, hypogonadism, and depression of immunity. The addition of zinc to lymphocyte cultures from immunodeficient patients in vitro increases the lymphocyte stimulating response to mitogens⁶. Zinc deficiency decreases cellular multiplication and thus, reduces T- and B-lymphocytes during both normal and antigen-stimulated conditions in humans and animals. Even though zinc deficiency results in expansion of undifferentiated T-lymphocytes, these are incapable of proper function. Natural killer cell and interleukin-2 activity is also known to be reduced in zinc deficiency. In humans, zinc deficiency results in selective decrease in the number of T4+ and CD8+CD73+ cells, as well as decrease in serum thymulin activity and T-lymphocyte proliferation⁷. Zinc supplementation to deficient people usually corrects the immunity problems⁸.

On the other hand, excess intake of zinc has been associated with reduction of lymphocyte-stimulated response, decrease in HDL, slight increase in LDL, copper deficiency, and low neutrophil counts⁹. High concentrations of zinc depress phagocytosis and microbicidal activity, perhaps by blocking membrane receptors, changing membrane fluidity and antagonistic effect on

other cations⁶. In vitro zinc concentration of 0.2 mM showed 97% bacterial killing and 100% oxygen consumption response by the neutrophils, but as the zinc concentration increased, the neutrophil activity went downhill⁶.

Association of Zinc with common cold

Since the role of zinc in immune function has been well established, it has been tested as a cure for common cold. This antiviral effect, however, was nonspecific. For this reason, zinc is supplemented to patients under immunosuppressive therapy especially for cancer. In 1979, George Eby observed his 3 year old daughter, who was undergoing chemotherapy for acute T-cell lymphocytic leukemia, to recover from a cold within several hours after dissolving a zinc gluconate tablet in her mouth rather than swallowing this tablet. This observation instigated Eby to conduct a clinical trial on the use of zinc gluconate lozenges for the treatment of the common cold. This trial¹⁰ reported efficacy of zinc lozenges in reducing cold symptoms but was criticized due to lack of lab monitoring, problems with placebo-matching, subjective measures and slightly mismatched treatment groups. Since then 10 double-blind controlled trials have followed all of which reported conflicting results.

Potential Mechanism of Action of Zinc in Reducing Cold Symptoms

The exact mechanism through which zinc affects the common cold remains to be determined.

There have been several speculations for potential mechanism of action of zinc:

—In vitro, at concentrations of about 0.1 mM, zinc prevents formation of viral capsid proteins, thereby inhibiting replication of several viruses, including the rhinovirus¹¹. Zinc has been shown to inhibit virus reproduction in HeLa cells infected with HRV-IA, but for RV-IA and RV-39 zinc salts had weak antiviral activity¹².

ICAM-1 is a glycoprotein and the major receptor for RV, through which the virus enters the cell¹³. ICAM-1 is involved in inflammatory processes by enhancing release of interleukins, cytokines and tumor necrosis factor or TNF¹³. Rhinovirus binds to ICAM-1 through a specific protein capsid. Zinc may combine with the carboxyl terminals (negatively charged surface canyons) of these proteins in the rhinovirus coat, which may prevent the virus from combining with the tissue-surface protein ICAM- 1 on the epithelium and thus, zinc may prevent viral entry into the cell. In vitro studies suggest that zinc may modulate immune system and in particular induce production of γ -interferons^{12,14} that may activate macrophage action, T-cell differentiation and stabilizing, and thus promote antiviral effects.

At concentrations of 0.01 to 0.1 mM, Zn⁺⁺ inhibits human prostaglandin metabolites, which may also account-for zinc's ability to relieve symptoms of the common cold².

Physiologic amounts of zinc may also be sufficient to reduce inflammatory response. Mast cell granules contain Zn⁺⁺, in addition to histamine, and the release of zinc from the lung mast cells has been suggested to play a significant role in the breakdown of histamine and termination of inflammation in colds¹⁵. In human serum, Zn⁺⁺ prevents histamine release from lung mast granules and basophils, and this anti-inflammatory effect may curtail upper respiratory tract infection symptoms.

- Zinc lozenges may exert a therapeutic effect by correcting a subclinical deficiency⁷. In a recent study in Indian children⁸, elemental zinc supplementation (10 mg/day for 20 days) resulted in a decrease in zinc deficiency and a 45% reduction in the incidence of acute respiratory infections. Berger¹⁶ showed that early trace element supplementation (Zn, Cu, Se) appeared beneficial after major burns and decreased the number of upper respiratory infections. This seems to be the most plausible mechanism of zinc's effect on common cold.

Clinical Trials Evaluating Efficacy of Zinc Lozenges to Cure Common Colds

Two different protocols are being used currently to study colds and other respiratory infections. First is the community-acquired infections to test treatment. This relies on subjective evaluation by the patients and not all community based colds are due to RV. The second protocol takes people out of community and puts them in a metabolic unit where they are kept under controlled conditions and then inoculated with a specific type of RV. Not all subjects develop infection and so only the ones who develop symptoms are studied. These trials usually include very few subjects. The virus challenge model and the natural cold model both have their advantages and disadvantages. Studies in different areas may be evaluating different viruses while all experimental models used rhinovirus challenge which does not give a complete picture. Even though inoculation studies provide controlled environment to study a specific virus-induced cold, there is evidence that upper respiratory tract infections from nasal inocula may have a different time-course than those obtained de novo. Therefore, it is hard to sum up the results from the two different approaches in evaluating cold symptoms at a specific point.

To date several placebo-controlled clinical studies of zinc as treatment for the common cold have been published. Of these, some have shown benefit of zinc lozenges^{5,10} while the other six did not show any benefit^{17,18}. The discrepancy in results have been attributed to the methodological flaws in these trials. The studies with negative results have used either zinc formulations that may render zinc ions inactive or had small sample sizes or may have used too low a dose of zinc. On the other hand, studies with positive results have been criticized for using placebo and active medications that did not taste alike (leading to inadequate blinding), or excluding too many patients from data analysis, or having small sample sizes, or using very subjective outcome measures. None of these studies measured zinc status of the subjects before putting them on zinc lozenges, thus it is difficult to establish the role of lozenges in correcting subclinical zinc deficiency.

The formulation of zinc lozenges used in some of these studies that failed to show a clinically significant benefit may have been responsible for the differences in results. Citric acid, tartaric acid, mannitol and sorbitol, which were added to improve the flavor of lozenges, may have caused chelation of Zn⁺⁺, thus inactivating the lozenges. While citric and tartaric acids are known to chelate Zn⁺⁺, the ability of sorbitol and mannitol to chelate Zn⁺⁺ in saliva is more controversial. Since a concentration of 0.1 mM of unbound Zn⁺⁺ is required for anti-rhinoviral activity of zinc in vitro^{12,19} it may be important for formulations of zinc lozenges to have the ability to produce adequate concentrations of unbound Zn⁺⁺.

The dose of zinc has also been attributed to the discrepancy of the study results. Weismann²⁰ used a dose of 4.5 mM elemental zinc and showed in vitro that this dose would produce more than 0.06 and less than 4.4 mM of Zn⁺⁺ in saliva. Since the exact mechanism of zinc action is not known, the concentration of Zn⁺⁺ required for efficacy in vivo and to evaluate the adequacy of doses used by different researchers is difficult.

In conclusion, the efficacy of zinc lozenges for treating common colds has yet to be proven.

Implications for Future Studies

To further investigate the role of zinc, if any, in treating the common cold, future trials need to address the following issues:

To ensure adequate blinding, perform taste-matching tests on placebo and zinc lozenges before the trial and test if patients can guess whether they are receiving the placebo or zinc. Zinc lozenges should be indistinguishable from the placebo.

- Test whether zinc lozenges transiently change Zn⁺⁺ concentration in nasal mucosa or even in oral cavity.

- From earlier studies, the adequate doses of bioavailable zinc seem to be at least 13 mg of elemental zinc. It is important to determine mechanism to setup an effective dose.
- Serum zinc levels should be measured before and after treatment to determine zinc status of individuals.
- Virologic studies should be obtained on all subjects including viral culture, viral shedding rate and duration.
- Determine T- and B-lymphocyte activity before and after the treatment, obtaining samples possibly through lung lavage. Other markers of immune function, such as interferon γ expression, histamine release and prostaglandin metabolites should be assessed.
- More objective outcome measures should be employed in assessing cold symptoms.
- Studies should have adequate sample sizes, close monitoring of cold symptoms and side effects during the study, and an intent to treat statistical analysis that includes all subjects initially enrolled in the trial to account for the dropouts.
- Careful monitoring for long term effects of zinc supplementation may also be useful.

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