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Zinc lozenges for the common cold

ABSTRACT

The scientific basis for zinc treatment of the common cold is debatable, and clinical trials of zinc cold therapy have produced conflicting results. This review summarizes the current basic and clinical knowledge of zinc for the common cold, and suggests the present role of zinc therapy and future research needs.

WE PHYSICIANS still have little to offer patients with the common cold, and nothing that definitely alters its natural history. These days, cold sufferers are rushing to buy zinc lozenges over-the-counter, encouraged by several studies that found them effective.[1–4] Yet, other studies[5–9] have concluded that zinc lozenges do nothing. In truth, we do not know with certainty whether zinc cures the common cold, nor do we know the mechanism of its possible action.

The following pages summarize what is and is not known about zinc as a cold treatment.

IF ZINC REALLY WORKS, HOW DOES IT WORK?

In theory, zinc could halt a common cold or reduce its symptoms by a variety of mechanisms.

- In vitro, at concentrations of about 0.1 mmol/L, zinc prevents formation of viral capsid proteins, thereby inhibiting replication of several viruses, including the rhinovirus.[10–15]
- Zinc may combine with the carboxyl terminals (negatively charged surface canyons) of proteins in the rhinovirus coat, which may prevent the virus from combining with the tissue-surface protein (intracellular adhesion molecule type 1) and entering the cell. This process stops further virus reproduction.[16,17]
- Extracellular zinc may stabilize and protect cell membranes against lysis by cytotoxic agents such as microbial toxins and complement, although the mechanism is uncertain.[14,18–21]
- In vitro studies suggest that zinc may modulate the immune system and in particular induce production of interferon.[11,17,22]
- At concentrations of 0.01 to 0.1 mmol/L, zinc ions inhibit human prostaglandin metabolites,[23] which may also account for zinc's ability to relieve symptoms of the common cold.
- Some have suggested that elevations of intranasal zinc salts might produce a "chemical clamp" on trigeminal and facial nerve endings, which would reduce sneezing, nasal discharge, and nasal congestion.[17]

Proof that zinc cures colds is lacking

Are these mechanisms biologically plausible? Some of them are only weak effects observed only in vitro. Moreover, we have no proof that zinc lozenges dissolved in oral saliva allow zinc ions to reach the area infected by common cold viruses, the nasal mucosa. For these reasons, some experts question whether the mechanisms outlined above could actually influence the course of the common cold in human beings.[18,22]

Do zinc lozenges correct a subclinical zinc deficiency?

Yet another hypothesis is that zinc lozenges exert a therapeutic effect by correcting subclinical zinc deficiency.[24]

Zinc deficiency is known to cause many

*The author owns stock in the Quigley Corporation, a manufacturer of zinc lozenges.

TABLE 1

Zinc in treating the common cold: Studies with positive results

INVESTIGATORS	NO. OF PATIENTS	FORMULATION	RESULTS (ZINC VS PLACEBO)	CONCERNS
Eby et al, 1984[1]	28	Zinc gluconate 23 mg	40% more colds resolved at 1 week (zinc 86%, placebo 46%; $P < .001$) 64% decrease in duration of colds (3.9 vs 10.8 days)	81 (55%) of 126 subjects enrolled excluded from analysis Poor comparability of placebo; possible unmasking Subjective outcome measures
Al-Nakib et al, 1987[2] (prophylactic trial)	14	Zinc gluconate 23 mg	33% lower clinical scores on day 4 ($P < .05$) No colds resolved No difference in nasal secretion weight or viral excretion	Small sample
Al-Nakib et al, 1987[2] (therapeutic trial)	12	Zinc gluconate 23 mg	Significantly better clinical scores on days 4 ($P < .01$) and 5 ($P < .05$) Lower nasal secretion weight on days 2 and 6 ($P < .05$)	Small sample
Godfrey et al, 1992[3]	73	Zinc gluconate glycine 23.7 mg	1.27 fewer days with colds ($P < .025$) Earlier treatment brought better improvement	Poor comparability of placebo; possible unmasking Subjective outcome measures Placebo effect noted
Mossad et al, 1996[4]	100	Zinc gluconate glycine 13.3 mg	42% fewer days with colds (7.6 vs 4.4 days; $P < .001$)	Poor comparability of placebo; possible unmasking Subjective outcome measures

abnormalities, including delayed wound healing, chronic diarrhea, growth failure, and immune deficiency.[24] In humans, zinc deficiency results in a selective decrease in the number of $T4^+$ and $CD8^+CD73^+$ cytolytic cells, as well as decreases in serum thymulin activity and T-lymphocyte proliferation.[25]

Giving zinc in physiologic amounts to zinc-deficient persons is an accepted practice.[24] In a double-blind, randomized, controlled trial in India in children with acute diarrhea,[26] zinc supplementation resulted in a 23% reduction in the risk of continued diarrhea and a 39% reduction in the mean number of watery stools per day. In another recent study in Indian children,[27] elemental zinc supplementation (10 mg/day for 120 days) resulted in a decrease in zinc deficiency and a 45% reduction in the incidence of acute lower respiratory infections.

Furthermore, nutritional zinc deficiency is prevalent throughout the world.[28–30] Cereal proteins contain large quantities of phytates, organic compounds that bind dietary zinc and render it unavailable for absorption. The shift away from consumption of red meat and toward consumption of cereal proteins containing high phytate levels may be conducive to the development of mild zinc deficiency in developed countries.[31] There are, however, no comprehensive data on the prevalence of zinc deficiency in the United States.

STUDIES ARE INCONCLUSIVE

To date, 11 double-blinded, placebo-controlled studies of zinc for treatment of the common cold have been published.[1–9,32] Of these, five studies found that zinc had beneficial effects (TABLE 1), and six did not (TABLE 2).

TABLE 2

Zinc in treating the common cold: Studies with negative results

INVESTIGATORS	NO. OF PATIENTS	FORMULATION	RESULTS (ZINC VS PLACEBO)	CONCERNS
Farr et al, 1987[5]	25	Zinc gluconate 23 mg with 2% citric acid	No difference in number, severity, or duration of symptoms No difference in nasal secretion weight, tissue count, or viral excretion	Small sample Formulation controversial; presence of free zinc ions questioned
Farr et al, 1987[5]	29	Zinc gluconate 23 mg with 2% citric acid	No difference in number, severity, or duration of symptoms No difference in nasal secretion weight, tissue count, or viral excretion	Small sample Formulation controversial; presence of free zinc ions questioned
Douglas et al, 1987[6] (prophylactic trial)	63	Zinc acetate 10 mg	No difference between groups	Formulation controversial; presence of free zinc ions questioned Placebo comparability questioned
Wisemann et al, 1990[7]	130	Zinc gluconate 4.5 mg	No difference in severity or duration of symptoms	Low dose of zinc; adequacy of concentration questioned
Smith et al, 1989[8]	140	Zinc gluconate 11.5 mg	No differences in duration of symptoms Severity reduced by 8% with zinc on days 5, 6, and 7 ($P = .02$) Adverse effects in 50% of zinc group	64 (37%) of 174 enrolled subjects were dropped from the study Effects not clinically important according to authors
Macknin et al, 1998[9]	249*	Zinc gluconate glycine 10 mg	No difference in severity or duration of symptoms	Low dose of zinc; adequacy of concentration questioned Subjective outcome measures Poor comparability of placebo; possible unmasking

*Children (median age 13)

To some extent, all the studies had flaws. The studies with negative results all used zinc formulations that may inactivate zinc salts, 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 subjective outcome measures.

Jackson et al[33] performed a meta-analysis of the eight studies available in 1997 and found that the evidence was inconclusive. These investigators excluded two studies that used nasal inoculation of rhinovirus because they were only interested in reviewing zinc's effects on naturally occurring colds. In the remaining six studies, the summary odds ratio for the presence of any cold symptoms at 7 days was 0.50—ie, persons were approximately half as likely to still have a cold a week later

if they took zinc lozenges. However, the difference was not statistically significant (95% confidence interval 0.19–1.29). The investigators concluded that "despite numerous randomized trials, the evidence for effectiveness of zinc salts lozenges in reducing the duration of common colds is still lacking."[33]

NEEDED: MORE, BETTER RESEARCH

Further research needs to be performed to determine accurately what role, if any, zinc has in treating the common cold. In this, I strongly concur with a recent editorial commenting on our negative study of zinc lozenges for treating the common cold in children: "The study by Macknin et al[9] by no means closes the door on zinc gluconate lozenges. Rather, it opens the field to more studies."[34]

However, future trials need to be designed better than the ones to date. Specifically, I would suggest the following:

- To ensure adequate blinding, we need to perform taste-matching tests on the placebo lozenges and the active medication before the clinical trials begin. Throughout the study, we need to ask the patients whether they can tell if they are receiving placebo or active medication, and include their responses in the analysis.
- Adequate doses of bioavailable zinc should be used, ie, at least 13 mg of zinc gluconate.
- Serum zinc levels should be measured before and after treatment.
- Virologic studies should be obtained on all enrollees.
- Standard scientific methodology must be used, ie, the studies should have adequate sample sizes, close monitoring of cold symptoms and possible side effects during the study, standardized outcome measures, few study participants lost to follow-up, and intent-to-treat analysis that includes all subjects initially enrolled in the trial.
- Careful monitoring for long-term effects of zinc supplementation should also be considered.

Until studies with the above characteristics are performed, the role of zinc treatment for the common cold will remain controversial.

WHAT DO WE TELL PATIENTS?

Lacking a definitive answer as to whether zinc is clinically helpful in relieving cold symptoms, what are we to tell our patients?

Zinc can have side effects, and care must be taken before generally suggesting zinc treatment to large numbers of cold sufferers. Acute side effects such as bad-taste reactions (a persistent bad taste or a taste so bad that the patient refuses to take the lozenges), nausea, and mouth irritation have been noted in published studies.[1,5,32] Though brief courses of zinc therapy have to date appeared to otherwise be safe, excess intake of zinc salts may result in a reduction of the lymphocyte-stimulation response, decreased concentrations of high-density lipoproteins, slight increases in low-density lipoproteins, copper deficiency, and low neutrophil counts.[35,36]

In children, no research has yet documented the effectiveness of zinc for colds.

In adults, the evidence is contradictory. It may be reasonable for adults to try zinc lozenges if they decide that their perceived benefit outweighs their side effects in treating this generally benign, self-limited condition. Some research suggests that zinc lozenges must be started during the first 24 hours of cold symptoms to be effective.[3]

Proof of safety is lacking with high-dose, long-term use

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