

Duration of Symptoms and Plasma Cytokine Levels in Patients with the Common Cold Treated with Zinc Acetate

A Randomized, Double-Blind, Placebo-Controlled Trial

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Background: Adults and children in the United States get two to six colds per year. Evidence that zinc is effective therapy for colds is inconsistent.

Objective: To test the efficacy of zinc acetate lozenges in reducing the duration of symptoms of the common cold.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: Detroit Medical Center, Detroit, Michigan.

Patients: 50 ambulatory volunteers recruited within 24 hours of developing symptoms of the common cold.

Intervention: Participants took one lozenge containing 12.8 mg of zinc acetate or placebo every 2 to 3 hours while awake as long as they had cold symptoms.

Measurements: Subjective symptom scores for sore throat, nasal discharge, nasal congestion, sneezing, cough, scratchy throat, hoarseness, muscle ache, fever, and headache were recorded daily for 12 days. Plasma zinc and proinflammatory cytokine levels were measured on day 1 and after participants were well.

Results: Forty-eight participants completed the study (25 in the

zinc group and 23 in the placebo group). Compared with the placebo group, the zinc group had shorter mean overall duration of cold symptoms (4.5 vs. 8.1 days), cough (3.1 [95% CI, 2.1 to 4.1] vs. 6.3 [CI, 4.9 to 7.7] days), and nasal discharge (4.1 [CI, 3.3 to 4.9] vs. 5.8 [CI, 4.3 to 7.3] days) and decreased total severity scores for all symptoms ($P < 0.002$, test for treatment \times time interaction). Mean changes in soluble interleukin-1 receptor antagonist level differed nonsignificantly between the zinc group and the placebo group (difference between changes, -89.4 pg/mL [CI, -243.6 to -64.8 pg/mL]).

Conclusion: Administration of zinc lozenges was associated with reduced duration and severity of cold symptoms, especially cough. Improvement in clinical symptoms with zinc treatment may be related to a decrease in proinflammatory cytokine levels; however, in this study, the observed differences between changes in cytokine levels in zinc and placebo recipients were not significant.

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Adults and children in the United States experience two to six colds per year (1, 2). The morbidity and loss of working hours due to the common cold are substantial (1-3), and treatment remains elusive. Ten controlled trials of treatment of the common cold with zinc lozenges have been published (4-13). Five studies reported that zinc lozenges reduced the duration of cold symptoms (4-8). The other five studies, however, showed no effect of zinc on cold symptoms (9-13). It has been argued that some studies did not find zinc to be effective because inadequate doses or incorrect formulations of zinc were used (13, 14).

No studies have elucidated the biochemical, immunologic, or virologic basis for zinc action. The most frequent cause of the common cold is rhinovirus infection; however, as many as 200 other viruses may be responsible for this condition (1, 2, 7). Korant and Butterworth (15) showed that zinc prevents the formation of viral capsid proteins and thus inhibits *in vitro* replication of several viruses, including rhinovirus. It has also been hypothesized that zinc

prevents the virus from binding with intracellular adhesion molecule 1 and thus from entering cells (16, 17). Two randomized, controlled trials examined viral shedding in volunteers who were inoculated with rhinovirus and were treated with zinc; the investigators concluded that zinc had no effect on this infection (9).

We determined the duration of cold symptoms in zinc-treated and placebo-treated participants. We also assayed plasma zinc and proinflammatory cytokine levels on the day 1 of the study and at the end of the resolution of cold symptoms in both groups.

Methods

Participants

We recruited 50 volunteers from Detroit Medical Center, Detroit, Michigan, to participate in a randomized, placebo-controlled trial of the efficacy of zinc acetate lozenges in treating the common cold. Two participants in

the placebo group dropped out on day 2. We therefore had complete data on 48 participants.

Participants were medical students, graduate and undergraduate students, staff, and employees at Wayne State University who were older than 18 years of age. Recruitment took place throughout 1998. Each volunteer was paid \$10 for participation and transportation costs. Participants were informed of the placebo-controlled, double-blind nature of the study, and the study protocol was approved by the Human and Animal Investigation Committee of Wayne State University.

Volunteers were recruited if they had had cold symptoms for 24 hours or less and had at least 2 of the following 10 symptoms: cough, headache, hoarseness, muscle ache, nasal drainage, nasal congestion, scratchy throat, sore throat, sneezing, and fever. We excluded persons who were pregnant, had a known immunodeficiency disorder, had a chronic illness, had had symptoms of the common cold for more than 24 hours, or had previously used zinc lozenges to treat the common cold.

We chose a sample size of 50 so that we could detect a difference in the mean number of days of symptoms from 8 days in the placebo group to 4 days in the zinc group with a standard deviation of 2 days, a two-sided *P* value of 0.05, and an approximate power of 80% or more. In view of Mossad and colleagues' findings (7), a 50% reduction in the duration of symptoms of the common cold in the treatment group was considered a reasonable end point.

Intervention

Each zinc lozenge consisted of 42.96 mg of zinc acetate dihydrate (USP) (Heico Chemicals, Delaware Water Gap, Pennsylvania), 6.0 mg of peppermint oil (National Formulary) (Bell Flavors, North Brook, Illinois), 16.0 mg of silica gel (National Formulary) (Siloid 244 FP, Davidson Chemical, Baltimore, Maryland), 4.0 mg of stevia extract powder (90% pure stevioside), 3835.04 mg of directly compressible dextrose (USP) (Unidex 2034), and 100 mg of glycerol monostearate (Myvaplex TM 600 P, Eastman Chemical, Kingsport, Tennessee). Each lozenge contained 12.8 mg of zinc. Each placebo lozenge contained 0.25 mg of sucrose octa acetate, 6.0 mg of peppermint oil, 16.0 mg of silica gel, 3877.75 mg of dextrose DC, and 100 mg of glycerol monostearate. The placebo and zinc lozenges were identical in weight (4000 mg), appearance, flavor, and texture.

A research consultant prepared the randomization code and the packages of medication (18). The packages were identical in appearance except for the randomization numbers. A research assistant who was blinded to treatment assignments distributed the study medication. Participants were given 50 lozenges and were asked to dissolve one lozenge in their mouths every 2 to 3 hours while awake for as long as they had cold symptoms. They were instructed to take no other cold preparations during the study period.

Outcome Measures

Our primary end point was the average duration of cold symptoms. Secondary end points were plasma levels of zinc and proinflammatory cytokines.

Participants were asked to complete a daily log documenting the severity of symptoms and the medications taken throughout the duration of the cold. Every day, the participants graded each symptom as 0 for none, 1 for mild, 2 for moderate, and 3 for severe. Total symptom scores were calculated by summing the scores of the 10 symptoms for each day. Resolution of cold symptoms was defined as resolution of all symptoms (a total symptom score of 0) or resolution of all but one mild symptom (a total symptom score of 1). The participants were not asked to rate their overall illness in terms of severity.

We obtained plasma samples for assay of zinc and proinflammatory cytokines. Zinc was assayed by using methods established in our laboratory that are based on atomic absorption spectrophotometry (19). Every precaution was taken to avoid contamination during collection, preparation, and analysis.

We measured levels of three proinflammatory cytokines before and after treatment: soluble interleukin-1 receptor antagonist, soluble tumor necrosis factor receptor, and neopterin. We also recruited 17 healthy adult volunteers with no symptoms of cold for a comparison assay of plasma proinflammatory cytokines and zinc.

Cytokines were analyzed by using enzyme-linked immunosorbent assay. Quantikine assay kits for soluble tumor necrosis factor receptor and soluble interleukin-1 receptor antagonist were obtained from R and D Systems, Minneapolis, Minnesota, and kits for analysis of neopterin were obtained from American Laboratory Products Company Ltd., Windham, New Hampshire. All cytokine assays were run on the same day.

To assess side effects of the treatment, participants were given a questionnaire to be filled out at the end of the trial. Participants provided “yes” or “no” answers to questions about nausea, vomiting, abdominal pain, diarrhea, constipation, dry mouth, bad taste, and mouth irritation.

Participants returned to the clinic for the final visit within 1 day of resolution of cold symptoms. At this time, they returned unused lozenges. This was done to check adherence and confirm that cold symptoms had resolved.

Maintenance of Blinding

Comparability in taste between zinc and placebo was tested in healthy volunteers. Ten participants were given a zinc lozenge and 10 received a placebo lozenge. One week later, the participants who received zinc were given placebo and those who received placebo were given zinc. At each visit, the participants filled out a questionnaire in which they were asked to guess whether they received a zinc or placebo lozenge. They had seven choices: certainly placebo, certainly zinc, do not know, possibly placebo, possibly zinc, probably placebo, and probably zinc. Volunteers who selected “certainly,” “probably,” or “possibly” and were correct about the type of lozenge they received were considered correct. We therefore categorized participants as “correct,” “incorrect,” or “do not know.”

We assessed the adequacy of blinding among study participants by administering the questionnaire used to assess comparability of taste in healthy volunteers. Parti-

Table 1. Demographic Characteristics of Study Participants*

Variable	Zinc Group (n = 25)	Placebo Group (n = 23)
Mean age \pm SD, y	36.4 \pm 11.1	37.8 \pm 10.9
Sex, n		
Male	7	11
Female	18	12
Ethnicity, n		
Black	5	11
White	19	12
Middle Eastern Arab	1	0
Smoker, n		
No	20	15
Yes	5	8
History of allergy, n		
No	23	19
Yes	2	4

* Twenty-five volunteers were initially recruited in each group. Two persons in the placebo group dropped out on day 2 and were lost to follow-up. One of the two persons had a sore mouth, and the other developed an ear infection for which care was transferred to a physician outside of Detroit Medical Center.

Table 2. Duration of Symptoms of the Common Cold

Variable	Mean Duration of Cold Symptoms (95% CI)		P Value
	Zinc Group (n = 25)	Placebo Group (n = 23)	
	<i>d</i>		
Overall symptoms*	4.5 \pm 1.6	8.1 \pm 1.8	<0.01
Specific symptomst			
Sore throat	2.0 (1.2 to 2.7)	3.0 (1.8 to 4.3)	>0.2
Nasal discharge	4.1 (3.3 to 4.9)	5.8 (4.3 to 7.3)	0.025
Nasal congestion	3.3 (2.3 to 4.3)	4.7 (3.1 to 6.2)	0.133
Sneezing	2.7 (1.9 to 3.5)	4.4 (3.0 to 5.9)	0.069
Cough	3.1 (2.1 to 4.1)	6.3 (4.9 to 7.7)	0.001
Scratchy throat	2.8 (1.9 to 3.7)	2.8 (1.4 to 4.2)	>0.2
Hoarseness	2.0 (1.0 to 3.0)	1.2 (0.3 to 2.7)	>0.2
Muscle ache	1.4 (0.6 to 2.2)	1.5 (0.3 to 2.7)	>0.2
Fever	0.4 (0.0 to 0.8)	0.2 (−0.1 to 0.5)	>0.2
Headache	2.0 (1.1 to 2.8)	2.4 (1.4 to 3.4)	>0.2

* Expressed as the mean \pm SD. The difference in overall duration of symptoms between groups was 3.6 days (95% CI, 2.6 to 4.6 days). Because the data on overall duration of symptoms were normally distributed according to the Shapiro–Wilk *W* test ($P = 0.13$ for both the zinc group and the placebo group; $P = 0.07$ when the groups were combined), a *t*-test was used to analyze the differences between groups.

† For each symptom, the Wilcoxon rank-sum test was used to determine differences between groups.

pants filled out the questionnaire at the beginning and at the end of the trial.

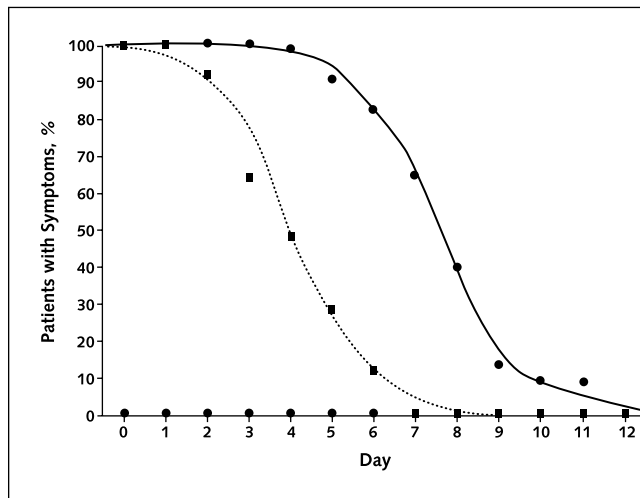
Statistical Analysis

We compared the change in outcomes before and after intervention in the zinc and placebo groups. When changes in both groups were normally distributed, as determined by using the Shapiro–Wilk *W* test, we used the *t*-test to compare mean changes. When they were not normally distributed, the differences between changes were compared by using the nonparametric Wilcoxon rank-sum test. Multivariate analysis of variance with repeated measures was used to determine the effect of treatment \times time on severity scores over the study period. The Fisher exact test were used to determine group differences in side effects. Chi-square analyses were performed to determine group differences in correctly identifying lozenges at baseline and after treatment.

The *t*-test was used to compare plasma zinc and cytokine levels before group assignment with levels in healthy controls. This was done to determine whether participants with colds differed from controls.

All statistical analyses were done by using JMP version 3.2.2 on a Macintosh computer (SAS Institute, Inc., Cary, North Carolina).

Figure 1. Duration of cold symptoms in the zinc group (squares) and the placebo group (circles).



Fifty percent of the zinc recipients were well in 3.8 days, and 50% of the placebo recipients were well in 7.7 days.

Role of the Funding Source

The George and Patsy Eby Research Foundation, Austin, Texas, donated unrestricted research funds to Wayne State University for partial support of this study. The research foundation had no role in the collection, analysis, or interpretation of the data or in the decision to publish the study. George Eby holds U.S. patent rights for zinc lozenges and donated funds earned from his patent rights to the research foundation. George Eby supplied zinc and placebo lozenges for this study. The authors have neither industry connections nor personal financial conflicts of interest related to the study.

Results

Table 1 shows the demographic characteristics of the study participants.

Duration and Severity of Cold Symptoms

The average duration of cold symptoms was 4.5 days in zinc recipients and 8.1 days in placebo recipients ($P < 0.01$) (Table 2). The duration of cough (6.3 and 3.1 days; $P < 0.001$) and nasal discharge (4.1 and 5.8 days; $P = 0.02$) was shorter in zinc recipients than in placebo recipients. Fifty percent of participants in the zinc group were well in 3.8 days, and 50% of the placebo group were well in 7.7 days (Figure 1).

The mean overall severity scores for cold symptoms are

shown in Figure 2. Repeated-measures analysis of severity scores indicated a treatment \times time interaction over the 12 days of the study ($P = 0.002$). At baseline, the average severity score was higher in the zinc group than in the placebo group (10.8 vs. 8.9). However, by day 4, the average severity score in the zinc group was half that in the placebo group (2.7 vs. 5.4).

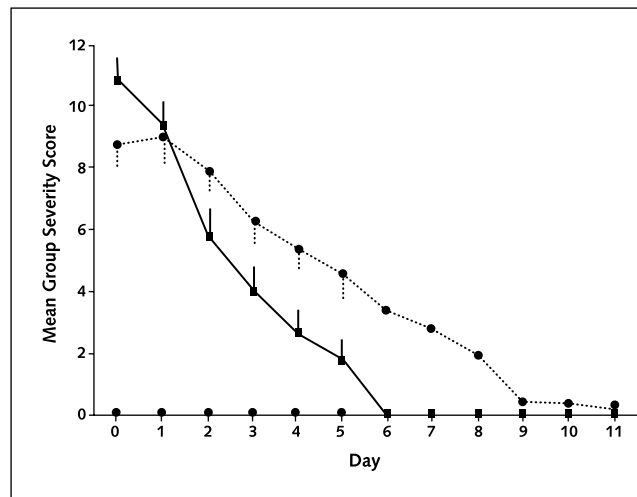
Adverse Effects

The zinc group and placebo group did not differ significantly in incidence of nausea (0 vs. 1 [0% vs. 4%]; $P > 0.2$), vomiting (0 vs. 0), abdominal pain (0 vs. 2 [0% vs. 9%]; $P > 0.2$), diarrhea (2 vs. 1 [8% vs. 4%]; $P > 0.2$), bad taste (13 vs. 6 [52% vs. 26%]; $P = 0.08$), or mouth irritation (10 vs. 4 [40% vs. 17%]; $P = 0.12$). Compared with placebo recipients, zinc recipients reported more mouth dryness (18 vs. 6 [72% vs. 26%]; $P = 0.003$) and constipation (6 vs. 0 [24% vs. 0%]; $P = 0.02$).

Adequacy of Blinding

Of 20 participants who received zinc, 5% correctly guessed that they were receiving active therapy. Of 20 participants who received placebo, 10% correctly guessed that they were receiving placebo. Therefore, participants did not correctly guess which type of lozenge they were receiving much better than by chance. In addition, at the begin-

Figure 2. Changes in severity scores after treatment in the zinc group (squares) and the placebo group (circles).



Values are given as the mean \pm SE. Repeated-measures analysis indicated a significant effect for treatment \times time between the zinc and placebo groups over the 12 days of the study ($P = 0.002$).

Table 3. Plasma Levels of Zinc and Proinflammatory Cytokines in Controls and Participants with the Common Cold

Variable	Before Treatment Assignment*		After Treatment Assignment**†				Mean Change		Between-Group Difference in Mean Change (95% CI)
	Controls‡	Patients with Cold on Study Day 1	Zinc Group		Placebo Group		Zinc Group	Placebo Group	
			Before Treatment	After Treatment	Before Treatment	After Treatment			
Plasma zinc level, $\mu\text{mol/L}$ (n)	14.3 (17)	14.6 (47)	14.8 (25)	17.7 (25)	15.1 (22)	14.3 (22)	2.9	-0.8	3.7 (2.2 to 5.0)
P value	0.2§						<0.001§		
Plasma cytokines									
Soluble interleukin-1 receptor antagonist level, pg/mL (n)	279.9 (17)	457.3 (39)	493.6 (22)	340.1 (22)	412.8 (17)	348.8 (17)	-153.5	-64.1	-89.4 (-243.6 to 64.8)
P value	0.022§						>0.2§		
Soluble tumor necrosis factor receptor level, pg/mL (n)	914.8 (17)	925.0 (37)	900.3 (20)	767.9 (20)	957.6 (17)	853.9 (17)	-132.4	-103.7	-28.7 (-222.7 to 165.3)
P value	>0.2§						>0.2§		
Neopterin level, pmol/mL (n)	3.6 (17)	6.5 (38)	6.1 (22)	4.9 (22)	7.0 (16)	5.9 (16)	-1.1	-1.1	0 (-3.2 to 3.2)
P value	<0.001§						0.2		

* Although duration of cold and specific symptoms was studied in 25 participants in the zinc group and 23 participants in the placebo group, blood samples were not available from all participants for laboratory analysis. The numbers in parentheses are the number of participants for whom data on zinc and cytokine levels were available.

† Only patients with cold on study day 1 were assigned to receive treatment or placebo.

‡ Healthy volunteers who were free of illness or cold.

§ Use of the Shapiro-Wilk W test revealed that the distribution of mean differences in the zinc and placebo groups in levels of zinc, soluble interleukin-1 receptor antagonist, and soluble tumor necrosis factor receptor were normal. Therefore, these variables were analyzed by using an unpaired *t*-test.

|| Use of the Shapiro-Wilk W test revealed that the distribution of mean differences in the zinc and placebo groups in levels of neopterin was not normal. Therefore, these variables were analyzed by using the nonparametric Wilcoxon rank-sum test.

ning of the trial, 48% of zinc recipients and 26% of placebo recipients correctly identified the lozenges ($P > 0.2$). At the end of the study, 56% of zinc recipients and 26% of placebo recipients correctly identified the lozenges ($P = 0.09$). None of these percentages exceeded 50%, indicating that blinding was adequate at the outset and was maintained throughout the study.

Proinflammatory Cytokines

Levels of proinflammatory cytokines in healthy controls and study participants with colds before group assignment are shown in Table 3. Only levels of soluble interleukin-1 receptor antagonist and neopterin were increased in participants with the common cold compared with healthy controls. Plasma zinc levels were normal in both groups.

The zinc and placebo groups differed significantly only in mean changes in plasma zinc level. The mean change in soluble interleukin-1 receptor antagonist level was greater in the zinc group than in the placebo group (-153.5 vs. -64.1 pg/mL), but this difference was not statistically significant ($P > 0.2$). The lack of significant difference in

mean changes in cytokine levels between the two groups may have been due to the fact that the blood samples were drawn approximately 3 days later in the placebo group than in the zinc group, after cold symptoms had resolved (the average duration of symptoms was 4.48 days in the zinc group and 8.1 days in the placebo group). The differences in mean changes in cytokine level between the two groups may have been more pronounced if blood for analysis had been drawn in the placebo group on day 5.

Adherence to therapy was determined by lozenge count. The average number of lozenges taken daily was 6.2 in the zinc group and 5.8 in the placebo group ($P = 0.2$).

Discussion

We found that treatment with zinc acetate lozenges was associated with a decrease in the average duration and severity of the common cold. Five previous trials failed to show a beneficial effect of zinc (9-13), perhaps because inadequate doses or inappropriate formulations of zinc were used, resulting in lack of bioavailable zinc (13, 14). Hatch and Berthon (20) reported that zinc acetate releases essentially 100% of its zinc as Zn^{2+} ions at a physiologic

pH. Thus, our use of zinc acetate lozenges may have been advantageous.

Except for mouth dryness and constipation, no statistically significant side effects occurred in zinc recipients compared with placebo recipients. The increased incidence of bad taste, mouth irritation, dry mouth, nausea, and gastric irritation found by Mossad and colleagues (7) and Eby and associates (4) may have been related to the use of different ligands (gluconate-glycine) rather than to zinc itself.

Proper blinding during a trial is important for interpretation of results (21). Our test in healthy controls showed that the zinc and placebo lozenges were indistinguishable in taste. Furthermore, in study participants, we observed no clear pattern of changes in the guesses, suggesting that adequate masking was maintained throughout the trial. Because the participants received only one type of lozenge, it is unlikely that differences in dryness of mouth would give them a basis for deciding whether the lozenge assigned to them contained zinc (22).

Some investigators (23, 24) have questioned the biological plausibility of the effectiveness of zinc lozenges as an antiviral agent for the cure of common cold. In our study, we did not culture viruses because the cost would have been prohibitive. Thus, we could not determine whether zinc had an antiviral effect. However, only zinc recipients experienced increases in plasma levels of zinc and changes in cytokine levels. Increased plasma concentrations of soluble interleukin-1 receptor antagonist, soluble tumor necrosis factor receptor, and neopterin have been observed in patients with infections (25–28). Increases in levels of these cytokines are known to be associated with activation of monocytes and macrophages as a general host response to infection or inflammatory stimuli (25–28).

Many of the symptoms observed in the common cold resemble the effects of proinflammatory cytokines (29–31). Fever, lack of appetite, leukocytosis, hypoferrremia, and induction of acute-phase reactant proteins are known effects of interleukin-1 production, a proinflammatory cytokine released by monocytes and macrophages in infection. Proinflammatory cytokines have been found in nasal secretions of patients with colds (32, 33), and production of cytokines has been detected in human rhinovirus-infected epithelial cells *in vitro* (32–34). As a result, the symptoms of the common cold are thought to result from an inflammatory “cytokine disease” (32). We previously showed that interleukin-1 β production by mononuclear cells is increased in zinc-deficient persons and is normalized

by zinc supplementation, suggesting that zinc modulates the proinflammatory cytokines released by macrophages and monocytes (35). In this study, we found that symptomatic improvement in the zinc group was associated with increased plasma levels of zinc, which may have modulated proinflammatory cytokines. However, we cannot rule out the possibility that the effect of zinc on macrophage and monocyte function may have been secondary to an antiviral effect.

Tremacamra, a soluble intercellular adhesion molecule 1 drug that functions as receptor blockade, was recently used to treat experimentally induced rhinovirus infection (36). Tremacamra was shown to be effective in decreasing the severity of common cold symptoms; however, it was not clear whether the duration of the cold was also decreased (36). In contrast, we found that zinc administration was associated with a decrease in the duration and severity of the common cold; zinc may therefore be a less expensive treatment option than tremacamra. In addition, zinc is nontoxic and is nonmutagenic, whereas the toxicity and mutagenicity of tremacamra remain to be ascertained.

Zinc-treated participants received approximately 80 mg of elemental zinc per day for 4 to 5 days, five times the recommended daily dietary allowance of 15 mg. Because this high dose was given for a short time, we believe that the effect of zinc was therapeutic and was not related to correction of zinc deficiency. As long as high-dose zinc was administered for a short time (for example, 5 days), it would be unlikely to cause copper deficiency. However, with indiscriminate use of high-dose zinc lozenges for 6 to 8 weeks, copper deficiency is likely to occur (37). Thus, zinc therapy for the common cold should be limited. We recommend that if a person does not show clear evidence of improvement after 3 days of zinc treatment, he or she should be investigated for other respiratory tract disorders or allergy and receive appropriate treatment.

In conclusion, treatment with zinc acetate lozenges was associated with reduction in the duration and severity of symptoms of the common cold. In addition, in zinc-treated participants, plasma levels of zinc increased and plasma levels of proinflammatory cytokines decreased. Improvements in clinical symptoms may be related to the effect of zinc on immunomodulation of proinflammatory cytokines.

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Christine Laine, MD, MPH
Deputy Editor