March 1997: 82–88

Zinc Lozenges Reduce the Duration of Common Cold Symptoms

A randomized, double-blind, placebo-controlled clinical trial has shown that treatment of the common cold with zinc gluconate lozenges resulted in a significant reduction in duration of symptoms of the cold. Patients received zinc-containing lozenges or placebo lozenges every 2 hours for the duration of cold symptoms. The median time to complete resolution of cold symptoms was 4.4 days in the zinc group compared with 7.6 days in the placebo group. The mechanism of action of zinc in treating the common cold remains unknown.

The common cold can be caused by more than 200 different viruses, including rhinovirus, coronavirus, adenovirus, respiratory syncytial virus, and parainfluenza virus. The most frequent cause of the common cold in adults is rhinoviruses. The ubiquitous common cold is one of the most frequently occurring diseases in the world. In the United States, adults usually develop two to four colds per year, while children have six to eight per year.[1] The search for an effective therapeutic agent against the common cold continues. A cold treatment that is even only partially effective in relieving cold symptoms could markedly reduce physical malaise and economic losses associated with the morbidity and lost working hours accompanying colds.

The effectiveness of zinc in the treatment of the common cold has been controversial. Eight double-blind, placebo-controlled studies have been published. Half of the studies have shown a beneficial effect of zinc treatment[1–4] and half have not.[5–8] The most recently published study of the efficacy of zinc in the treatment of the common cold was conducted by Mossad et al.[1] at the Cleveland Clinic in Cleveland, Ohio, among volunteers studied between early October and November 1994.

Editors' Note: Readers should know that this article, which has not, to our knowledge, been challenged with respect to its scientific accuracy or its peer review, has been the subject of subsequent discussion of a possible conflict of interest.

Mossad and colleagues[1] enrolled 100 subjects (all employees of the Cleveland Clinic) who reported cold symptoms for 24 hours or less. The patients had to have had at least two of the common cold symptoms listed in Table 1 to meet the enrollment criteria. Exclusion criteria were pregnancy, known history of immune deficiency, and cold symptoms for greater than 24 hours.

Patients were randomized to either zinc treatment or placebo in a double-blind study design. The zinc treatment consisted of zinc-containing lozenges. The zinc lozenges were a boiled hard-candy base prepared with equal proportions of sucrose and corn syrup, as well as zinc gluconate trihydrate, a molar proportion of glycine, and lemon and lime flavoring oils. The zinc-containing lozenges had 13.3 mg zinc per lozenge. The placebo lozenges were prepared from the same flavored hard-candy base and contained 5% calcium lactate pentahydrate. The placebo and zinc-containing lozenges were reported to have identical physical characteristics. However, organoleptic properties of the two lozenges did differ, since the zinc-containing lozenges were more astringent. Nonetheless, masking appears to have been maintained in this study because neither the placebo group nor the zinc group correctly guessed that they were getting the active medication.

Patients were given 120 lozenges each and were asked to dissolve one lozenge in their mouth every 2 hours while awake for as long as they had cold symptoms. All subjects were given oral thermometers and acetaminophen. Patients were instructed to take no other cold medications during the study. Patients returned to the clinic within 1 day of resolution of their cold symptoms. At this time they returned the unused portion of lozenges, and the resolution of cold symptoms was confirmed by the study nurse. During the study period the patients completed a daily log documenting the severity of 10 symptoms (see Table 1) and the medications taken throughout the duration of their colds for up to 18 days.

A four-point grading scheme of cold symptom severity was employed: 0 for none, 1 for mild, 2 for

Table 1. Common Cold Symptoms Measured in the Zinc Study

Cough
Headache
Hoarseness
Muscle aches
Nasal drainage
Nasal congestion
Scratchy throat
Sore throat
Sneezing
Fever (oral temperature > 37.7 °C)

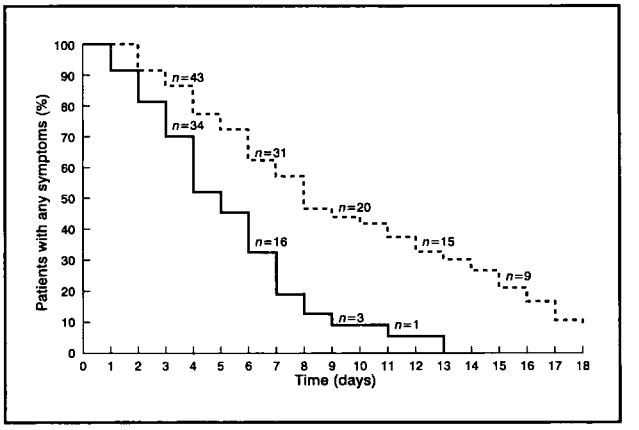

Figure 1. Kaplan-Meier curve for the duration of colds. Solid line = zinc group; dotted line = placebo group. From Mossad et al.[1] and used here with permission.

moderate, and 3 for severe. Total symptom scores were calculated by summing the score for the 10 symptoms each day. Resolution of the cold was defined as cessation of all symptoms, i.e., a total symptom score of 0, or resolution of all but one mild symptom, a total symptom score of 1. For analysis of treatment effect, the symptom list was reduced from 10 symptoms to 7 by combining the symptoms of hoarseness, sore throat, and scratchy throat into a category called "throat symptoms." Likewise, nasal drainage and nasal congestion were combined into "nasal symptoms."

Patient adherence to treatment was calculated as the number of lozenges consumed based on the total count of returned medication. As a result of a treatment effect on the duration of the cold symptoms, the placebo group took a mean total of 49 ± 30 lozenges (median 42) and the zinc group took a mean total of 36 ± 22 lozenges (median 28). However, the number of lozenges taken per day (median 5) did not differ between the two groups, nor did the use of acetaminophen differ between the two study groups . Despite the warning not to use other cold medications during the study, 15 patients (10 placebo, 5 zinc group) took other cold medications. Statistical analysis was done using an intention-to-treat framework, regardless of patient adherence. Patients who received antibiotic treatment or whose condition was diagnosed by a physician as an illness other than the common cold were considered nonadherent. Patients who wrote their diaries from memory were also considered nonadherent. Patients were considered adherent if they took 4 or more lozenges per day for the first 4 days of the study and if they took no antibiotics. One patient withdrew from the study on the first day because of intolerance to the zinc-containing lozenge. The demographic characteristics of the remaining 99 subjects were similar in the placebo and zinc treatment groups.

The median symptom scores at baseline were the same for both groups. The mean symptom score was slightly greater in the placebo group compared with the zinc treatment group, 9 versus 8, respectively. However, 6 hours after the study began the mean symptom scores were 9.3 ± 4.2 for placebo and 8.7 ● 4.0 for the zinc group. None of the subjects in the study had a fever at baseline. Analysis of the prevalence of individual symptoms at baseline showed that a significantly greater portion of the placebo group (78%) reported a sore throat compared with the zinc-treated group (51%). Likewise, there was a tendency ($p < 0.09$) for fewer patients to report sneezing in the placebo group (62%) compared with the zinc group (78%).

All but eight of the patients had colds that resolved while they remained in the 18-day study. The median time to resolution of all cold symptoms was 7.6 days in the placebo group and 4.4 days in the zinc group, indicating a significantly faster resolution of cold symptoms in the zinc group ($p < 0.001$). The effect of zinc treatment can be seen in Figure 1, which shows the percentage of patients with a cold on each of the 18 study days (Kaplan-Meier curve).

Seventeen of the 100 patients were considered nonadherent (10 in the zinc group and 7 in the placebo group). Of these 17, 6 did not take enough medication for reasons that were not stated, 5 stopped taking the medication because of adverse effects attributed to the lozenges (all of these patients were taking the zinc-containing lozenges, 4 took antibiotics, 2 reconstructed their diaries from memory, and 2 stopped keeping their diaries for unstated reasons. When the data were reanalyzed after excluding these 17 nonadherent subjects, the study conclusions remained the same. Cold symptoms in the zinc group still resolved faster than they did in the placebo group ($p < 0.001$).

Analysis of the treatment effects on each cold

symptom indicated that the zinc-treated group had significantly fewer days with any symptom, nasal symptoms, throat symptoms, coughing, headache, hoarseness, nasal congestion, nasal drainage, and sore throat. No significant difference in the groups was found for resolution of muscle ache, scratchy throat, sneezing, or fever. Surprisingly, subjective assessment of whether the treatment received had any effect on relieving symptoms of the cold revealed no difference between the two groups, despite the positive effects of the zinc treatment on the duration of cold symptoms.

Side effects from the medication were assessed in two ways. During the study, the subjects were asked an open-ended question wherein they listed all of the side effects of the medication they were taking. Seventeen of the 49 subjects taking the zinc-containing lozenges reported that no side effects developed with their medications before the conclusion of the study. A comparison of duration of cold symptoms in this subgroup compared with that in the 32 patients in the zinc group who reported some side effect of the lozenge found no significant difference in the duration of cold symptoms. Thus, perception of a medication-related side effect did not influence the reporting of duration of the cold symptoms within the zinc group.

In a second method of assessing the influence of medication-associated side effects on the reported duration of cold symptoms, the investigators asked the subjects at the end of the study whether any of a list of specific side effects were present. Patients in the zinc group reported significantly more side effects per person. Half of the subjects in the zinc group reported two or more of the listed symptoms, whereas only 10% of the placebo subjects did so. Subjects taking the zinc-containing lozenges reported significantly more nausea and more bad-taste reactions.

The positive findings of Mossad et al.[1] in reducing the duration of common cold–related symptoms in adult subjects are similar to the findings of three other previously published studies, but are in conflict with four other published reports where no positive effect of zinc treatment was observed. Of the three other studies showing a positive treatment effect of zinc,[2–4] Eby et al.[2] found that at 7 days of treatment, 54% of the placebo group still had cold symptoms compared with only 14% in the zinc-treated group. However, the high number of zinc-treated patients experiencing adverse side effects of their medication has led to questions about the effectiveness of masking in this study.[5] Al-Nakib and colleagues[3] investigated the effects of zinc lozenge treatment on experimentally induced cold symptoms. They found no apparent effects of giving zinc lozenges prophylactically, but they noted a reduction in clinical scores on days 4 and 5 of treatment. In this study, the placebo lozenge was not distinguished from the zinc lozenge by taste or appearance. Finally, Godfrey et al.[4] found a 42% reduction in duration of cold symptoms compared with the placebo group when zinc gluconate-glycine lozenge treatment was begun on the first day of cold symptoms. If treatment was withheld until the second day of cold symptoms, a 26% reduction in cold duration was evident with zinc treatment.

The four studies that found no effect of zinc treatment on cold symptoms have been challenged[9–11] on the basis of poor bioavailability of the zinc lozenge preparations, either due to a proposed failure of the lozenge formulations to provide adequate amounts of free zinc ions to the saliva and oral tissues[5–7] or due to doses of zinc in the lozenge that were below a possible therapeutic threshold.[8]

The current study by Mossad et al.[1] was designed primarily as a practical demonstration of the efficacy of zinc lozenge treatment on duration of common cold symptoms, and the authors admit to several limitations of their study. No microbiological diagnosis of the common cold was obtained. The authors suggest that the timing of studies of this nature could have a critical effect on the study outcome. The timing of their study in October preceded the influenza season. Moreover, the absence of fever in the patients at baseline suggests that certain viruses, such as influenza, parainfluenza, and adenovirus, were unlikely causes of the colds in their patients. A significant difference in baseline symptoms between the placebo and zinc groups (sore throat and possibly sneezing) may indicate that different viruses were responsible for the colds in the two groups; however, this difference between the groups diminished within the first 12 hours of the study. There was no chemical verification of compliance to the two dosing regimens. Furthermore, the results of this study do not necessarily apply to either pregnant women or immunocompromised patients because these patient groups were excluded from the study.

No information is provided by this study concerning the cumulative effects of repeated uses of zinc or the development of resistance to treatment. Habitual use of large doses of zinc can cause imbalances in levels of other minerals, such as copper. Doses of 75 mg of zinc or more can effectively inhibit copper absorption in humans and are used clinically to lower copper absorption in patients with Wilson's disease, a copper overload disorder.[12] These investigators avoided using doses of zinc that would

supply more than 150 mg/day (10 times the RDA), which have been associated with adverse effects on the immune system.[13] The current study did not analyze for a possible beneficial effect of the zinc treatment on systemic immune response. No immune function tests were performed during the study.

The clinical studies to date that have investigated the efficacy of zinc lozenges in treating the common cold have provided no information about the mechanism by which zinc is effective in reducing the duration of cold symptoms. Some of the possibilities suggested include an effect of zinc to prevent formation of viral capsid proteins, which could inhibit the replication of virus; a possible effect of zinc to stabilize and protect cell membranes; enhancement of interferon production; and inhibition of prostaglandin metabolism. Additional clinical study of the efficacy of zinc treatment to alleviate symptoms of the common cold still appear warranted, as are studies into the possible mechanism of action of the zinc effect. Presumably, a better understanding of the mechanism of zinc's beneficial effects on cold symptoms could lead to the development of even more efficacious strategies that would be useful in the treatment or perhaps even prevention of this annoying malady.

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Neuropeptides Responding to Leptin

Leptin, the circulating protein that inhibits food intake and energy expenditure, was thought to function through inhibition of the hypothalamic neuropeptide Y (NPY), a stimulator of food intake. However, mouse mutants lacking NPY are normal, suggesting that alternative neuromodulators of food intake must exist. Recently, melanocortin, a neuropeptide acting on the hypothalamic receptor melanocortin4-R, was discovered in mice, controlling energy regulation. This receptor is antagonized by the "agouti" protein in the mutant obese agouti mouse.

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Mice develop obesity and diabetes (type II) as a result of a single recessive mutation.[1] The gene responsible, the *ob* gene, normally encodes a circulating protein hormone (OB protein, or leptin), secreted by adipocytes in the fat deposits both in mice and in humans.[2,3] When recombinant leptin purified from *Escherichia coli* is injected into ob/ob mice, it lowers their weight and plasma glucose level.[4] In normal mice, leptin administration reduces weight and corrects diet-induced obesity.[5] Human and mouse leptins are highly homologous, with 84% sequence identity,[2] and both are equivalent in weight-reducing power in mice, with losses mainly of body fat. In the mouse, leptin controls both food intake and energy expenditure,[6] thus acting as a hormone that provides weight homeostasis.