Zinc Gluconate Lozenges for Treating the Common Cold in Children
A Randomized Controlled Trial

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Context.—The common cold is one of the most frequently occurring illnesses and is responsible for substantial morbidity and economic loss. Biochemical evidence suggests that zinc may be an effective treatment, and zinc gluconate glycine (ZGG) lozenges have been shown to reduce the duration of cold symptoms in adults.

Objective.—To determine the efficacy of ZGG treatment of colds in children and adolescents.

Design.—A randomized, double-masked, placebo-controlled study.

Setting.—Two suburban school districts in Cleveland, Ohio.

Patients.—A total of 249 students in grades 1 through 12 were enrolled within the first 24 hours of experiencing at least 2 of 9 symptoms of the common cold.

Intervention.—Zinc lozenges, 10 mg, orally dissolved, 5 times a day (in grades 1-6) or 6 times a day (in grades 7-12).

Main Outcome Measures.—Time to resolution of cold symptoms based on subjective daily symptom scores for cough, headache, hoarseness, muscle ache, nasal congestion, nasal drainage, scratchy throat, sore throat, and sneezing.

Results.—Time to resolution of all cold symptoms did not differ significantly between students receiving zinc (n = 124) and those receiving placebo (n = 125) (median, 9 days; 95% confidence interval [CI], 8-9 days; median, 9 days, 95% CI, 7-10 days, respectively; P = .71). There were no significant differences in the time to resolution of any of the 9 symptoms studied. Compared with controls, more students in the zinc group reported adverse effects (88.6% vs 79.8%; P = .06); bad taste (60.2% vs 37.9%; P = .001); nausea (29.3% vs 16.1%; P = .01); mouth, tongue, or throat discomfort (36.6% vs 24.2%; P = .03); and diarrhea (10.6% vs 4.0%; P = .05).

Conclusions.—In this community-based, randomized controlled trial, ZGG lozenges were not effective in treating cold symptoms in children and adolescents. Further studies with virologic testing are needed to clarify what role, if any, zinc may play in treating cold symptoms.

THE COMMON cold is one of the most frequently occurring illnesses in the world. More than 200 viruses can cause common colds in adults, including rhinoviruses (the most frequent cause), coronaviruses, adenoviruses, respiratory syncytial virus, and parainfluenza viruses. In the United States each year, adults have an average of 2 to 4 colds and children have an average of 6 to 8 colds.1,2 The morbidity resulting from these illnesses and the subsequent financial costs in terms of loss of time from work are substantial.3 Previously described treatments have provided neither consistent nor well-documented relief of symptoms. However, even a treatment that is only partially effective in relieving cold symptoms could markedly enhance recovery and reduce economic losses in a large population.

Different formulations of oral zinc have been evaluated as a cold remedy. Ten double-masked, placebo-controlled clinical trials have been reported, but each used a different dose or formulation of zinc. Five of these studies showed that zinc had a beneficial clinical effect and 5 found no effect.4-11 Zinc treatment had no effect on viral shedding.12,13 All studies reported to date have been performed on adults.

For editorial comment see p 1999.

METHODS
Study Design

This study was similar in design to a previous study of zinc for cold treatment in adult patients at the Cleveland Clinic Foundation.7 The current study is a prospective, randomized, double-masked, placebo-controlled investigation designed to assess whether zinc gluconate glycine (ZGG) lozenges would reduce the time to resolution of cold symptoms in children (Figure 1).

Subject Recruitment and Enrollment Criteria

The study was approved by the Cleveland Clinic institutional review board. Presentations were made to school administrators and school boards in the communities, and their permission to conduct the study in the school systems was obtained.

Students were recruited from the Beachwood and Mayfield school districts in the eastern suburbs of Cleveland, Ohio, during the winter cold season, from October 7, 1996, through March 13, 1997. Before enrollment began, students willing to participate in the study were identified by responses to a consent form and...
sonel offices: before school, at lunchtime, and before school was dismissed. If the students did not come to the office to receive their medication, the study personnel went to their classes to distribute it. If students missed school, they were instructed to take their regularly scheduled medications from their home medication package. Students in grades 1 through 6 were instructed to take 2 lozenges at home on school nights and 5 lozenges per day at home on weekends. Students in grades 7 through 12 were instructed to take 3 lozenges at home on school nights and 6 per day at home on weekends. Students were instructed to let the lozenges dissolve in their mouths and not to chew them. Patients were asked to take study lozenges until their cold symptoms had been completely resolved for 6 hours.

Adherence and Outcome Measures

Adherence was assessed by a daily diary of the medication taken and by the number of lozenges returned at the end of the study. Whenever there was a discrepancy between the diary and medication returned, the number of lozenges returned was used. Based on the duration of the cold, the number of prescribed lozenges was calculated. Adherence was defined as taking at least 70% of the prescribed medication.

Students were given exactly enough lozenges for 3 weeks of treatment, 126 and 105 lozenges for secondary and elementary students, respectively. However, students were followed up until their cold symptoms resolved, even if their symptoms persisted beyond 21 days. They were asked to take no other cold preparations, if possible, during the study. Oral digital thermometers were given to students at the time of enrollment. All students had a brief examination at the time of enrollment by trained study personnel, who confirmed the presence of at least 1 sign of a cold (cough, hoarseness, nasal drainage, nasal congestion, throat redness and exudate, enlarged tonsils, and sneezing), and another brief examination at discharge from the study. Cold symptoms, adverse effects from medications, and other medications taken were recorded daily on school days by the study personnel who distributed the lozenges. On non-school days and missed school days, students phoned all information into a voice mail recording. If study personnel did not receive a voice mail message, they called students at home.

Students graded each symptom on a numerical scale of 0 to 3 each day, but parents occasionally questioned the symptom rating assigned by students. In cases of dispute, the parent’s evaluation was used instead of the child’s. Students reported daily on the severity of 9 symptoms: cough, headache, hoarseness, muscle ache, nasal drainage, nasal congestion, scratchy throat, sneezing, and sore throat. Severity for each symptom was measured as either none (0), mild (1), moderate (2), or severe (3). The overall severity score was computed as the sum of severity scores of all 9 symptoms, yielding a number between 0 and 27. Resolution of the cold was defined as the time at which the total severity score reached 0, indicating the absence of all symptoms. On day 2 and on the final day of the study, students were asked to guess whether the medication they were taking was “active drug, placebo, or don’t know.” We identified adverse effects by each day asking students an open-ended question about adverse effects and by offering a list of potential adverse effects to choose from at the conclusion of the study.

Zinc Lozenges

The ZGG and placebo lozenges were supplied by the Quigley Corporation. The zinc lozenges consisted of a hard-candy base prepared with approximately equal proportions of sucrose and
Ten students’ (3 placebo, 7 active) colds did not resolve during the period of observation. Thus, statistical methods for incomplete data were used. Resolution rates were calculated using the method of Kaplan and Meier,14 and 95% confidence intervals (CIs) for the estimates of median time to resolution were calculated using the method of Brookmeyer and Crowley.15

The primary analyses of resolution time were performed using Cox proportional hazards regression models16 and the method devised by Efron17 to adjust for the large number of patients with identical resolution times. The suitability of a proportional hazards model was first assessed by modeling resolution time as a function of treatment group and as a time-dependent factor representing an interaction between treatment group and time. Although the observed hazards were not strictly proportional, the extent of non-proportionality was not statistically significant (P = .64). Two students, who were determined to be ineligible after assignment, were included in these analyses, in keeping with the intent-to-treat principle, and were treated as censored observations with a cold duration of 0.001 days. Estimates of the effect of treatment group assignment on the probability of school absence on a given day were obtained using generalized estimating equations.18

Adverse effects, success of masking, medication use, and adherence were compared between groups using \( \chi^2 \) tests, unless the expected cell frequencies were small, in which case the Fisher exact test was used. In all cases, \( P \) values of .05 or less were considered to be statistically significant. All statistical analyses were performed using software from the SAS Institute, Cary, NC, and were independently verified by 2 biostatisticians (M. P. and J. J.).

### RESULTS

#### Demographic Information

A total of 249 students received either ZGG lozenges (n = 124) or an identically packaged placebo (n = 125). Baseline characteristics were similar between the 2 groups (Table 1). Distributions of race and sex within the students on the study (overall, 92.4% white, 4.0% black, and 3.6% other, and 52.2% female) were similar to those of the entire school population (88.0% white, 7.3% black, and 4.7% other, and 48.4% female). Baseline characteristics of the students, including prevalence of allergies, proportion who smoked, frequency of colds and other infections, and temperatures between 37.1°C and 37.7°C were similar between the groups (Table 1). The only characteristic for which there was an imbalance was asthma. Seventeen (14%) of 120 patients in the placebo group and 9 (7.5%) of 120 in the zinc group reported a history of asthma (P = .10). (Cox regression analysis revealed that this imbalance had no significant effect on time to cold resolution.)

Medications used by the groups at enrollment were similar. However, 31 subjects (25.0%) in the zinc group and 20 subjects (16.0%) in the placebo group were taking vitamins or mineral supplements (P = .08). At enrollment, all students were asked to discontinue taking any zinc-containing vitamins or mineral supplements during the course of the study.

Two students reported that they deliberately provided false information at enrollment because they wanted to participate in the study with their friends who had colds. In keeping with the intent-to-treat principle, these students were included in the primary analyses of time to resolution of symptoms, but they were excluded from secondary analyses and from the tables involving initial symptoms. The proportion of students with each initial symptom, and the results of comparisons between groups are shown in Table 2. The distributions of symptoms in the 2 groups were similar, except that fewer students in the zinc group presented with cough (71.8% vs 58.5%, P = .03).
The median score for overall severity of initial symptoms, computed as the sum of the initial scores for each symptom, was 10 (range, 3-22; mean ± SD, 10.1 ± 3.9) for the placebo group, vs 9 (range, 2-22; mean ± SD, 9.2 ± 3.9) for the zinc group. This difference was statistically significant (P = .03), but not clinically important because an increase of 1 point in total symptom score represents an increase of 1 level of severity for 1 symptom or 1 additional mild symptom. The severity score 6 hours later was available for 231 patients; the placebo group had a mean score of 8.7 ± 4.35 and a median of 8, and the zinc group had a mean of 7.7 ± 4.1 and a median of 7 (P = .09).

Resolution of All Symptoms

The median time to resolution of all cold symptoms was 9.0 days (95% CI, 8.9-9 days) in the placebo group and 9.0 days (95% CI, 7.10 days) in the zinc group (P = .71; Figure 2). In the elementary grades, 57 students who received placebo and 56 students who received zinc experienced resolution of all symptoms in a median of 9.0 days (95% CI, 8.11 days) and 8.0 days (95% CI, 7-10 days), respectively (P = .44). In the junior and senior high schools, 68 students who received placebo and 68 students who received zinc had a median time to resolution of all symptoms of 8.5 days (95% CI, 7-9 days) and 9.5 days (95% CI, 7-10 days), respectively (P = .89). The lack of statistical differences between the groups remained (P = .73) after adjusting for age and initial severity of illness level.

For 8 students (5 aged 7 years, 2 aged 8 years, and 1 aged 9 years) in whom their symptom ratings disagreed with their parents' ratings, the parents' evaluation was used.

Resolution of Individual Symptoms

Separate models were also fit to assess whether the resolution time of individual symptoms was related to treatment group. Because the presence and severity of individual symptoms often fluctuated during the course of the cold, for these analyses, the symptom was considered to be resolved when the score for that symptom reached 0 for the last time, or until the last day the patient was seen if it had not resolved. Treatment groups had no significant effect on the time for resolution of any of the individual symptoms (Table 3).

Table 3.—Median Time to Resolution of Cold Symptoms Among 249 Students Treated With Zinc Gluconate Glycine Lozenges or Placebo

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Placebo (n = 125)</th>
<th>Zinc (n = 124)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom No.</td>
<td>Median Time to Res, d (95% Confidence Interval)</td>
<td>Median Time to Res, d (95% Confidence Interval)</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>89</td>
<td>8 (6-9)</td>
<td>72</td>
</tr>
<tr>
<td>Headache</td>
<td>55</td>
<td>5 (4-7)</td>
<td>57</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>65</td>
<td>5 (4-6)</td>
<td>52</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>109</td>
<td>8 (7-9)</td>
<td>103</td>
</tr>
<tr>
<td>Nasal drainage</td>
<td>107</td>
<td>7 (6-8)</td>
<td>99</td>
</tr>
<tr>
<td>Muscle ache</td>
<td>34</td>
<td>4 (3-6)</td>
<td>31</td>
</tr>
<tr>
<td>Scratchy throat</td>
<td>77</td>
<td>5 (4-6)</td>
<td>68</td>
</tr>
<tr>
<td>Sore throat</td>
<td>74</td>
<td>4 (4-5)</td>
<td>64</td>
</tr>
<tr>
<td>Sneezing</td>
<td>88</td>
<td>6 (5-7)</td>
<td>79</td>
</tr>
<tr>
<td>All symptoms</td>
<td>125</td>
<td>9 (7-10)</td>
<td>124</td>
</tr>
</tbody>
</table>

* Cox regression analysis.

School Absences

There were a total of 85 days of school absence in the 2,454 days (1260 placebo, 1194 active) the students were in the study, including 53 days of absence (among 26 children) in the placebo group, and 32 days of absence (among 23 children) in the zinc group. Children taking zinc were therefore less likely to be absent than children taking placebo (odds ratio, 0.69; 95% CI, 0.32-1.13), but this difference was not statistically significant (P = .12).

Adverse Effects

Slightly more students in the zinc group (n = 109) experienced at least 1 adverse effect than in the placebo group (n = 99). The students who received zinc experienced significantly more bad taste reactions; nausea; mouth, tongue, or throat irritation; and diarrhea than those in the placebo group; there were no significant differences in the frequency of vomiting, abdominal pain, constipation, dizziness, headache, or dry mouth between the groups (Table 4).

Adherence to the Protocol

The median percentage of prescribed lozenges taken was 83.3% overall and did not differ significantly between groups (83.3% in the placebo group and 82.5% in the zinc group, P = .45). Overall, 74.1% (183/247) of subjects took at least 70% of the medication prescribed; 73.4% (91/124) of the placebo group and 74.8% (92/123) of the zinc group (P = .80). Forty-six percent (57/124) of the placebo group and 47.2% (58/123) of the zinc group reported taking more lozenges, by a median of 6 lozenges in both groups, than verified by pill counts; no patients underreported the number of lozenges taken. The extent of misreporting was not significantly different between the groups (P = .29 by Wilcoxon rank sum test).

If the zinc lozenges had a beneficial effect, students in the zinc group with the highest adherence rates would be expected to have the shortest duration of symptoms; however, the proportional hazards regression model found no statistically significant association (P = .36) between adherence and duration of symptoms, and there was also no statistically significant association (P = .33) between the dose of zinc per body surface area per day and duration of symptoms. Excluding all nonadherent patients from the data analysis did not change the results that the median time to resolution of all symptoms was 9 days (95% CI, 8-10 days) in the placebo group and 9 days (95% CI, 7-10 days) in the zinc group and was not statistically different (P = .48).

Assessment of Masking

Students were asked to indicate whether they thought they were taking the active drug, the placebo, or whether they didn’t know on day 2 and at the conclusion of the study. Defining the guesses on day 2 and at the end of the study as either correct or incorrect (which included the response of “don’t know”), 35% (85/242) of the patients guessed correctly on day 2. A significantly higher proportion of students receiving zinc (46% [55/119]) guessed correctly than did controls (24% [30/123]; P = .001) on day 2. At the end of the study the results were similar, with 56% (67/119) of students receiving zinc guessing correctly vs 42% (51/123) of...
controls (P = .02). Six patients who had previously taken Cold-Eeze were inadvertently enrolled in the study. Of these 6, 1 of 3 taking placebo and 1 of 3 taking zinc correctly identified their study medication. When we performed the analysis excluding students with the “don’t know” responses (n = 103 students on days 2 and 41 at the end of the study), the results similarly showed that students who received zinc were more likely to guess their group assignment than those receiving placebo.

COMMENT

Ten previous double-masked, placebo-controlled studies of zinc for treatment of the common cold have been reported.1-11 Half of these studies reported beneficial effects of zinc1-7 and half did not.8-11 The major criticisms of the studies with negative results are that the formulations of zinc used may inactivate zinc salts, the studies had small sample sizes, and too low a dose of zinc was used. Studies with positive results have been criticized for inadequate masking because of poor taste matching of placebo and zinc medications, too many patients being excluded from data analysis, small sample sizes, and subjective outcome measures. The controversies over the efficacy of zinc treatment for the common cold are summarized in a recent meta-analysis.19 The doses and formulations of zinc used, clinical settings, number and type of patients, and possible shortcomings and results of these studies have varied widely.19

The mechanisms by which zinc may affect the common cold remain to be determined, but several possibilities have been suggested. Zinc prevents the formation of viral capsid proteins, thereby inhibiting in vitro replication of several viruses, including rhinovirus.20-24 Zinc ions combine with the carboxyl termini (negatively charged cations) of rhinovirus coat proteins, which may prevent the virus from combining with the tissue-surface protein (intracelllular adhesion molecule type 1) and entering the cell. Inhibition of entry of virus into the cell stops further reproduction.25,26 Extraceular zinc also may exert antiviral effects by stabilizing and protecting cell membranes by an unknown mechanism.27-30 In vitro studies have suggested that zinc may induce the production of interferon.27 Zinc ions also have properties that inhibit human prostaglandin metabolism at 0.01 to 0.1 mmol,28 which may also allow zinc to help relieve symptoms of the common cold.

Two studies with different doses of the same formulation of ZGG lozenges in adults found a 42% decrease in the duration of symptoms with zinc treatment29,30 compared with placebo. The discrepant results between these studies in adults and the current study in children may be explained by the different dosages or flavors of the formulation, the ages of the subjects, the time of year when the studies were performed (ie, the viruses involved may have been different), or chance differences between the placebo and zinc groups.

The first study in adults of the same formulation of ZGG that we studied for the common cold was conducted in college students.6 The dosages of 23.7 mg was given about 8 times per day; this was more than 3 times the dose used in the current study. The second study in adults was conducted in hospital employees.3 A dose of 13.3 mg was given approximately 6 times per day. In the current study, a dose of 10 mg was administered 5 or 6 times a day, so that the children’s doses would be approximately proportional in milligrams per square meter of body surface area to the dose used in the second study6 in adults. Also, the dosage of zinc used in the first study in adults achieved intraoral zinc concentrations well in excess of those needed to inhibit rhinovirus in vitro.29,30 Despite what seems to be a sufficient dosage, the dosage in our current study may have been too low for children and adolescents. Because the mechanism(s) of action of zinc in treating the common cold is unknown, the optimal dose of medication is also unknown. In another study of zinc gluconate performed in adults, no beneficial effect was found using a dose of 4.5 mg.11 The current study used cherry-flavored lozenges, whereas the adult study used lemon-lime–flavored lozenges. It is possible that the cherry flavoring in some unknown way inactivated the zinc.

Mild subclinical zinc deficiency, present predominantly in adults, may impair cellular immunity; accordingly, zinc supplementation might enhance cellular immunity in adults.25,26 Arguing against this explanation is the fact that 1 of the 2 previous studies using the same formulation of zinc that we used in the current study was done in college students6 whose ages were closer to many of the students in the current study than to the adults in our previous study.7 Furthermore, a study of another zinc preparation reported increased serum zinc levels without a decreased length of common cold symptoms.3

Students may have been less subject to a “placebo effect” if they were less able than adults to guess which substance they were receiving. This explanation seems unlikely because students guessed their group assignments more accurately than did the adults, and subjects’ guesses about which medication they were receiving were not associated with their response to treatment in either study. Students’ ability to more accurately “break the blind” than adults would, if anything, be expected to bias results in favor of a beneficial effect of treatment in the current study.

Adherence is another issue that might have influenced the results. If zinc were beneficial, but students were less adherent than adults, the beneficial effect would not be observed. However, the students were more closely monitored to ensure adherence in this study than in either of the 2 previous studies performed in adults; both diaries and pill counts in this study reflected good adherence. Furthermore, there was no statistically significant correlation between days to symptom resolution and either dosage of zinc in milligrams per square meter of body surface area per day or adherence.

Viruses may vary in their susceptibility to zinc. Theoretically, zinc ions may be most effective against rhinovirus,26 which is most prominent at both ends of the respiratory season.7 Our study was
performed throughout the cold season. The previous 2 studies each enrolled patients over approximately 1 month, one near the beginning and the other near the end of the cold season. Although we did not perform diagnostic viral studies, rhinovirus almost certainly would not have been the predominant virus isolated throughout this entire study. In a subgroup analysis, students who were enrolled in October (n = 51) were analyzed separately and compared with adults who had been enrolled at about the same time of year in the previous trial of zinc gluconate in Cleveland, but the effect of zinc treatment in reducing cold symptoms was nonsignificant (P = .63). However, the small number of patients involved (ie, those enrolled in October) may have been insufficient to demonstrate a difference, even if one were present.

We investigated the effect of asthma on outcome because more students receiving placebo had asthma than those students receiving zinc, and also assessed whether the higher rate of vitamin use in the group receiving zinc influenced the outcome. Cox regression analysis showed that neither asthma nor vitamin use significantly influenced outcome. Considering the placebo group had statistically significantly higher symptom scores at baseline and more coughs (which may be related to the higher incidence of asthma in the placebo group) at baseline than the zinc group should, if anything, bias the results toward a beneficial outcome in the zinc group.

The current study has several limitations. First, students, particularly in the early elementary grades, may not have reliably reported their symptoms. However, with a few exceptions, it was our impression that the students were reliable. Second, we did not evaluate objective measures of cold severity, such as tissue counts or nasal mucus weight, because of the impracticability of obtaining these measures in our student population, and because we believed symptom scores were the most important outcome measure. Although virus cultures or serologic assays might have been desirable, we decided not to perform these tests because of their cost and because they are seldom performed in the course of standard care. Also, the placebo lozenges used in our study were not exactly the same as the zinc lozenges; however, any bias resulting from patients correctly guessing their assigned study medication would have favored assessments showing efficacy of zinc lozenge treatment. We also studied only 1 dose of zinc lozenges (which was lower than doses previously shown to be effective against cold symptoms), and we studied only 1 formulation of zinc lozenge.

In conclusion, ZG lozenges in the dosages studied were ineffective in relieving cold symptoms in children and adolescents in this placebo-controlled, randomized, community-based trial. Additional studies in all age groups with different dosages and formulations of zinc lozenges and with virologic testing are needed to define what role, if any, zinc has in the treatment of common cold symptoms.

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