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.


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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.1 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

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Dr Macknin owns 20,000 shares that he acquired in December 1996 in a private placement upon the exercise of stock options granted by the Quigley Corporation.

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cover letter from school administrators and the principal investigator, which were mailed to all parents and guardians of children in the study schools. The principal investigator and study personnel attempted to contact the family of every potential enrollee by telephone to answer any questions about the study. The principal investigator spoke about scientific research in general and the study in particular to most science classes in the participating high schools and middle schools. School-based study personnel collected consent forms. As an incentive, all students who returned signed consent forms were entered into a raffle with a grand prize of a trip for 4 to a popular theme park or the cash equivalent. Students did not have to become ill and be enrolled in the study to be eligible to win the raffle. Only students with informed consent forms on file at school and signed by their parents or guardians (for students younger than 18 years) were eligible for enrollment in the study. Study personnel enrolled patients before school, at lunchtime, and at the end of the school day, or in the patients’ homes if they were contacted on non-school days, during the first 24 hours of the student’s cold symptoms.

Students were required to report having at least 2 of the following 9 symptoms: cough, headache, hoarseness, muscle ache, nasal congestion, nasal drainage, scratchy throat, sore throat, or sneezing. Students were excluded if they had an oral temperature greater than 37.7°C, had previously taken zinc, or had a known immune deficiency. Other reasons for exclusion were an acute illness other than the common cold (eg, pneumonia, gastroenteritis) or an acute illness other than the common cold preparations, if possible, during the study. Oral digital thermometers were given to students 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...
corn syrup, zinc gluconate trihydrate (AKZO Chemie, Amersfoort, the Netherlands), a molar proportion of glycine (aminoacetic acid), and cherry flavoring oils. The mixture was formed into lozenges that weighed 3.75 g and contained calcium lactate pentahydrate instead of zinc. Placebo lozenges were prepared from the same flavored hard-candy base and contained calcium lactate pentahydrate instead of zinc. Placebo and active lozenges were as identical to assess whether the response to ZGG lozenges (n = 124) or an identically packaged placebo (n = 125). Baseline characteristic 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 subjects were asked to discontinue taking any zinc-containing vitamins or mineral supplements during the course of the study.

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, and 95% confidence intervals (CIs) for the estimates of median time to resolution were calculated using the method of Brookmeyer and Crowley.

The primary analyses of resolution time were performed using Cox proportional hazards regression models and the method devised by Efron 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.

Adverse effects, success of masking, medication use, and adherence were compared between groups using χ² 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
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 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, 9-10 days) and 8.0 days (95% CI, 6-11 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 = .88). The lack of statistically significant 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).

**School Absences**

There were a total of 85 days of school absence in the 2454 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, 0.60; 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% (182/247) 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”), 85% (211/247) of the patients guessed correctly on day 2. There was no significant difference in the proportion of students guessing correctly (P = .001) on day 2. At the end of the study the results were similar, with 56% (67/119) of the placebo group and 52% (51/123) of the zinc group, P = .45. Overall, 74.1% (182/247) 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).

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>No.</td>
<td>Median Time to Resolution, d (95% Confidence Interval)</td>
<td>No.</td>
<td>Median Time to Resolution, d (95% Confidence Interval)</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.

Figure 2.—Time to resolution of all cold symptoms among students treated with zinc gluconate glycine lozenges or placebo.
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.4-7 Half of these studies reported beneficial effects of zinc4-7 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 dosages 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 cysteans) of rhino-

### Table 4.—Frequency of Adverse Effects Experienced by Students With Cold Symptoms During Treatment With Zinc Gluconate Glycine Lozenges or Placebo

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Placebo, No. (%) (n = 124)</th>
<th>Zinc, No. (%) (n = 123)</th>
<th>Total, No. (%) (n = 247)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bad taste</strong></td>
<td>47 (37.9)</td>
<td>74 (60.2)</td>
<td>121 (49.0)</td>
<td>.01</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>20 (16.1)</td>
<td>36 (29.3)</td>
<td>56 (22.7)</td>
<td>.01</td>
</tr>
<tr>
<td><strong>Irritation</strong></td>
<td>30 (24.2)</td>
<td>45 (36.6)</td>
<td>75 (30.4)</td>
<td>.03</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>5 (4.0)</td>
<td>13 (10.6)</td>
<td>18 (7.3)</td>
<td>.05</td>
</tr>
<tr>
<td><strong>Dizziness</strong></td>
<td>11 (8.9)</td>
<td>16 (13.0)</td>
<td>27 (10.9)</td>
<td>.30</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>31 (25.0)</td>
<td>25 (20.3)</td>
<td>56 (22.7)</td>
<td>.38</td>
</tr>
<tr>
<td><strong>Abdominal pain</strong></td>
<td>32 (25.8)</td>
<td>36 (29.3)</td>
<td>68 (27.5)</td>
<td>.54</td>
</tr>
<tr>
<td><strong>Dry mouth</strong></td>
<td>33 (26.6)</td>
<td>37 (30.1)</td>
<td>70 (28.3)</td>
<td>.55</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>3 (2.4)</td>
<td>4 (3.3)</td>
<td>7 (2.8)</td>
<td>.72</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td>2 (1.6)</td>
<td>2 (1.6)</td>
<td>4 (1.6)</td>
<td>.99</td>
</tr>
<tr>
<td><strong>Nasea</strong></td>
<td>20 (16.1)</td>
<td>16 (13.0)</td>
<td>36 (14.6)</td>
<td>.49</td>
</tr>
<tr>
<td><strong>Any adverse effect</strong></td>
<td>95 (78.8)</td>
<td>106 (86.6)</td>
<td>201 (81.2)</td>
<td>.06</td>
</tr>
</tbody>
</table>

*Mouth, tongue, or throat discomfort or irritation.

†Some examples of other adverse effects include chills, drowsiness, bloody nose in the placebo group and ears popping, tired, watery eyes in the active group.

*Viruses may vary in their susceptibility to zinc. Theoretically, zinc ions may be most effective against rhinovirus, which is most prominent at both ends of the respiratory season.*

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performed throughout the cold season. The previous 2 studies each enrolled pa-
tients 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 iso-
lated throughout this entire study. In
a subgroup analysis, students who were
enrolled in October (n = 51) were ana-
yzed separately and compared with
those who entered in November (n = 51).
They were of the same age, sex, and
race, and although this comparison was
not 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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