

An Open-Label, Single-Center, Phase IV Clinical Study of the Effectiveness of Zinc Gluconate Glycine Lozenges (Cold-Eeze) in Reducing the Duration and Symptoms of the Common Cold in School-Aged Subjects

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Each year, more than 62 million cases of the common cold in the United States require medical attention and more than 80% affect school-aged children. The objective of this prospective, intent-to-treat, phase IV study was to determine the therapeutic and prophylactic effectiveness of zinc gluconate glycine lozenges (Cold-Eeze) for the common cold. Zinc lozenges were administered once daily during the cold season for prophylaxis. For therapeutic purposes, lozenges were given 4 times per day. The primary objective of the study was the treatment effect on cold duration, and the secondary objective was the effect on the number of common colds. A putative control from our previous study was used for comparison. A total of 178 children, ages 12 to 18 years, was enrolled, of which 134 met criteria for efficacy analysis. The average cold duration with therapeutic lozenge use was 6.9 ± 3.1 days, significantly shorter than the 9.0 ± 3.5 days found in the control group ($P < 0.001$). The mean number of colds was 1.28 ± 1.03 with zinc lozenge prophylaxis versus 1.7 ± 1.91 without prophylaxis ($P < 0.05$), a 25% reduction. With prophylaxis, 25% of the subjects did not experience a cold and two-thirds never had a cold or only had 1 cold. There was no antibiotic use for any cold, and there were no adverse events reported. Results of this study are consistent with those from our previous retrospective study showing significantly shorter cold duration and fewer colds with the use of zinc gluconate glycine lozenges. The zinc gluconate glycine lozenges are well tolerated and are an easy-to-administer therapy that has the potential to substantially reduce cold-related school absences and antibiotic use and misuse as well as to provide a cost saving.

Keywords: cold, prophylaxis, treatment, prospective, zinc gluconate glycine lozenges, Cold-Eeze

INTRODUCTION

The common cold is characterized by symptoms of rhinorrhea, nasal obstruction, sneezing, throat clearing, postnasal drip, and cough.¹ Colds are among the most common illnesses, and it has been estimated that individuals in the United States suffer approximately 1 billion colds each year.² While many adults self-medicate to manage cold symptoms,³ a large number of colds in children and adolescents require

medical attention. Statistics indicates that more than 52 million colds in individuals younger than 18 years of age required medical attention in 1996.^{2,4} The indirect costs associated with colds are extremely high. One recent study estimated that each cold experienced by a working adult caused an average of 8.7 lost work hours. In addition, 1.2 work hours were lost because of the need to attend to each cold episode in a child younger than 12 years of age. This resulted in an annual lost productivity cost of \$25 billion, of which \$230 million was due to caring for children with colds.⁵

Approximately 50% of colds are caused by human rhinoviruses,⁶ and there is scarce conclusive evidence that they are effectively prevented or treated by antibiotics, currently available antiviral drugs, or other remedies, such as inhaled corticosteroids, large doses of vitamin C, or echinacea.⁷⁻¹¹

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Recent clinical studies have shown that ionic zinc (Zn^{2+}) can shorten the duration of cold symptoms and reduce the number of colds experienced by school-aged children.¹²⁻¹⁵

The primary objective of the current study was to evaluate the effectiveness of zinc gluconate glycine lozenges (Cold-Eeze) in reducing the duration and severity of the common cold in a school-aged population. The secondary objective was to determine the benefits, if any, of prophylactic administration of zinc gluconate glycine lozenges in reducing the occurrence of the common cold.

METHODS

Study design

The rationale for an open-label methodology was based on several factors. The Heritage Center data already indicated that mandatory symptomatic cold treatment with zinc gluconate glycine lozenges to children exhibiting cold signs and/or symptoms as well as the prophylactic administration of 1 zinc gluconate glycine lozenge daily to all healthy children reduced illness, the number of school days lost, and medical costs at the school. A double-blind, placebo-controlled clinical study in which some children would not have received active medication would have jeopardized the improvements already achieved in cold reduction and duration. Additionally, a double-blind, placebo-controlled study would have required the school to segregate the population and alter the day-to-day activities of the children. Since the Heritage Center did not use zinc gluconate glycine lozenges for the treatment of colds before 1999, it was reasonable that the retrospective data collected from that time period could serve as a "placebo" control. Therefore, using a historical (putative) control was a reasonable approach.

For prophylaxis, zinc gluconate glycine lozenges were administered once daily during the cold season, identified for the purposes of this study as October 5, 2001 to May 30, 2002. Lozenges were also given 4 times per day at the onset of cold signs and/or symptoms until symptoms resolved.

Setting

The Heritage Center of Provo, UT, is a placement facility that monitors and rehabilitates children between 12 and 18 years of age with histories of mental illness, substance abuse, social disturbances, and general difficulties in daily interaction with peers, family, or so-

ciety. Approximately 150 residents are housed at any given time.

Subjects

Inclusion criteria

Both male and female residents, 12 to 18 years of age, were eligible for the study. All were required to be in overall good health, as determined by the investigator, and willing to comply with clinical study procedures.

Exclusion criteria

Subjects were excluded if they were pregnant or lactating, were taking concomitant prophylactic antibiotic therapy, or had used an antibiotic within 7 days of study entry. Also excluded were subjects unwilling or unable to comply with clinical study procedures and study product dosing, those with a history of sensitivity or idiosyncratic or other adverse experience with zinc or other ingredients of the study product, or those who had been treated with any other investigational product within 30 days of the first dose of study product.

Procedures

Eligible subjects received a single daily zinc gluconate glycine lozenge beginning on October 5, 2001 and ending May 30, 2002. The dose was increased to 4 lozenges per day in subjects who exhibited 2 predetermined signs and/or symptoms consistent with the common cold. These included sneezing, cough, postnasal drip, hoarseness, sore throat, and stuffy nose. Subjects rated the severity level of cold signs and symptoms on a 4-point scale (0 = absent, 1 = mild, 2 = moderate, and 3 = severe). Subjects received zinc gluconate glycine lozenges 4 times per day until signs and/or symptoms resolved (i.e., absence of all signs and/or symptoms or resolution of all but 1 mild sign or symptom); cold signs and/or symptoms were monitored twice daily. Cold resolution was based on subject-reported documentation in the medical chart, cessation of zinc gluconate glycine lozenge therapy because it was no longer required, or medical staff documentation of absence of cold signs and/or symptoms.

Efficacy evaluation

Efficacy was evaluated by determining cold duration and severity of cold signs and/or symptom occurrence, ratings, and resolution. The effectiveness of zinc gluconate glycine lozenges was assessed in evaluable subjects. Excluded were subjects who received antibiotic therapy 7 days before cold signs and/or

symptoms and those who had taken less than 50% of their prophylactic dosage or less than 50% of their therapeutic dosage during cold treatment.

The ability of zinc gluconate glycine lozenges to reduce cold duration was determined by comparing the cold durations in this study population and those observed in our previous retrospective study.¹³ In the retrospective study, the durations of 239 colds without zinc gluconate glycine lozenges therapy (control) and 232 colds with lozenge therapy were evaluated. The retrospective study also evaluated the prophylactic effect of zinc gluconate glycine lozenges in 377 patients without prophylaxis (control) and in 119 patients with prophylaxis.

Antibiotic use was captured to corroborate findings from the previous chart review study, which indicated there was no negative impact on subjects when zinc gluconate glycine lozenges were administered at the first sign of cold signs and/or symptoms rather than antibiotics. Subjects who were on prophylactic antibiotic therapy for other indications were excluded from the study. If subjects discontinued prophylactic antibiotic therapy, they were eligible for enrollment after a 7-day washout period.

Safety evaluations

The safety of treatment with zinc gluconate glycine lozenges was determined by recording adverse events, defined as untoward clinical events or worsening of preexisting conditions judged by the investigator to be related, probably related, or possibly related to study treatment. The duration of all adverse events was recorded, and events were rated as mild, moderate, or severe.

Serious adverse events were designated as those that resulted in death, were life threatening, required inpatient hospitalization or prolonged hospitalization, resulted in persistent or significant disability or incapacity, or were a congenital anomaly.

Statistical methods

Descriptive statistics were used for analysis of demographic and other baseline information. The efficacy end points were analyzed by ANOVA (SPSS software package, Version 10) using the least significant difference (LSD) for post hoc multiple comparison. Differences were considered statistically significant at $P < 0.05$.

RESULTS

Subjects

The study included 178 subjects. The demographic characteristics of these subjects are summarized in

Table 1. Overall, 80% ($n = 143$) completed the study; 35 (20%) discontinued, nearly all ($n = 30$) for noncompliance. Of the 143 subjects who completed the study, a total of 134 subjects met the criteria for the evaluability of efficacy. Excluded were subjects who received antibiotic therapy 7 days before cold signs and/or symptoms, those who had taken less than 50% of their prophylactic dosage, or those who had taken less than 50% of their therapeutic dosage during cold treatment.

Efficacy

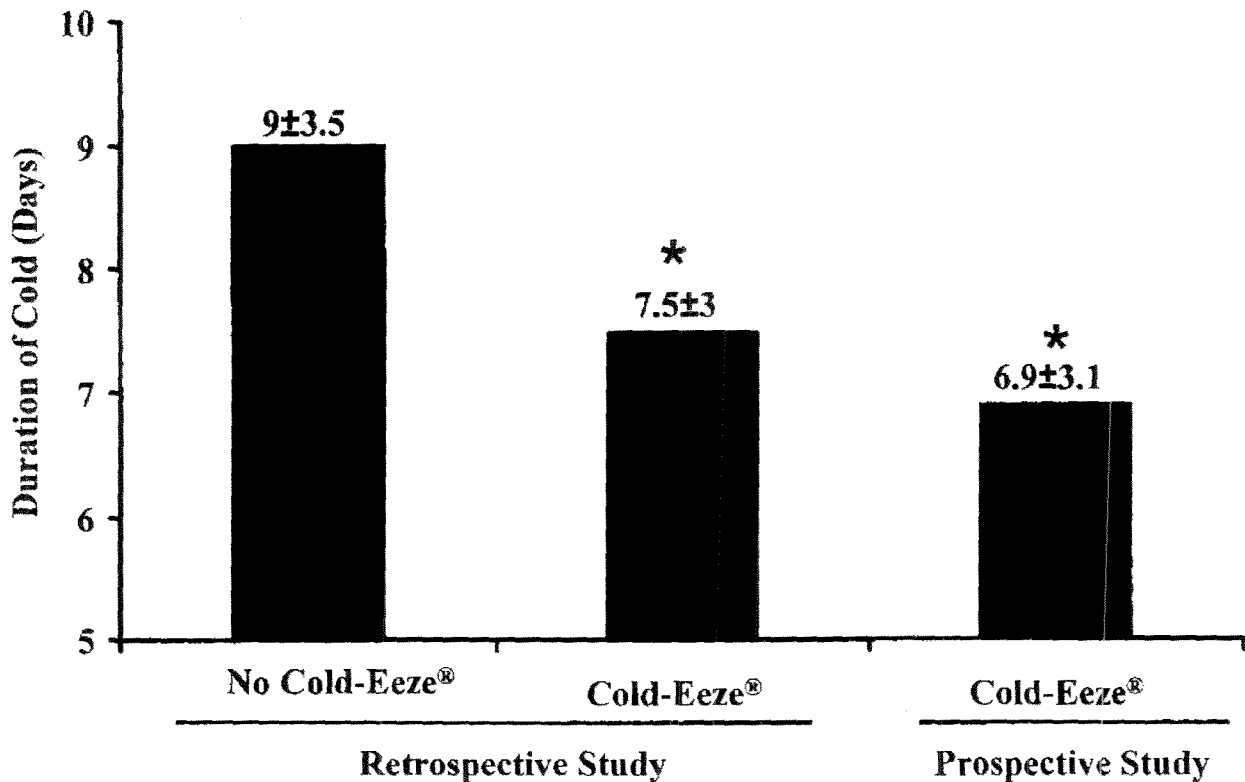
Effect of zinc gluconate glycine lozenges on cold duration

A total of 139 colds met the evaluation criteria. The mean duration of colds was 6.9 ± 3.1 days, which is significantly shorter than the mean cold duration of 9.0 ± 3.5 days ($P < 0.001$) for those subjects not given zinc gluconate glycine lozenges in the retrospective study (Fig. 1). The average cold duration was 7.5 ± 3.0 days for those given zinc gluconate glycine lozenges in the retrospective study. Cold durations were significantly shorter with therapeutic use of zinc gluconate glycine lozenges in both the current and the retrospective studies compared with the no treatment group ($P < 0.001$).

Figure 2 shows the frequency distribution of the durations of colds. The most frequently observed cold duration was 5 days with zinc gluconate glycine lozenges therapy in the current study (same as in the retrospective study with therapeutic lozenges use), whereas it was 11 days in the retrospective study without zinc gluconate glycine lozenges therapy.

Table 1. Characteristics of enrollees.

Characteristics	Percentage of subjects (N = 178)
Male/female	56/44
Race	
Caucasian	66
Black	8
Hispanic	10
Native American	3
Asian	1
Other	12
Age (yr)	
12	2
13	12
14	16
15	19
16	32
17	19



* $p < 0.001$ compared to no cold Cold-Eeze® therapy

FIGURE 1. The effect of zinc gluconate glycine lozenge therapy on cold duration. Cold durations were significantly shorter with the therapeutic use of zinc gluconate glycine lozenges in both the current and the retrospective studies compared with the no treatment group ($P < 0.001$). While cold duration was shorter in the current prospective study than in the retrospective study with zinc lozenge therapy, the difference was not statistically significant.

Effect of zinc gluconate glycine lozenges on the number of colds

The average number of colds was 1.28 ± 1.03 per subject with the prophylactic use of zinc gluconate glycine lozenges in this study. This is significantly fewer than the 1.7 ± 1.9 colds per person without prophylaxis in the retrospective study ($P < 0.05$). With zinc gluconate glycine lozenge prophylaxis, there were no statistically significant differences in the number of colds between the current and retrospective studies.

Twenty-five percent of subjects never experienced a cold during the 2001 to 2002 cold season, with 39% experiencing 1 cold with prophylaxis. Approximately two-thirds never had a cold or only had 1 cold, and 99% had 3 or fewer colds. Combined, these results illustrate that the prophylactic use of zinc gluconate glycine lozenges significantly lessen the occurrence of the common cold in this age group.

Antibiotic use

There was no antibiotic use for the treatment of colds in this study. This is consistent with the results of the

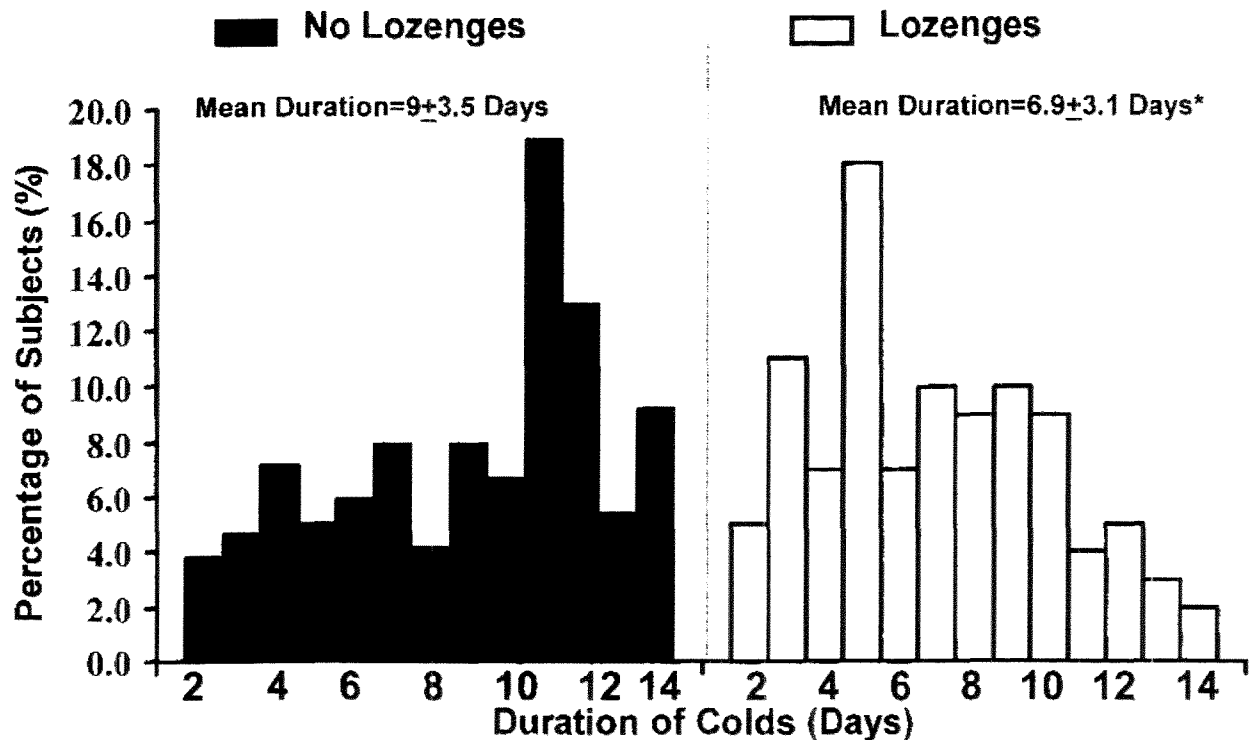
retrospective study. With the therapeutic use of zinc lozenges, only 3% of the colds required concomitant antibiotic therapy, which is dramatically less compared with the 39% of colds not treated with zinc lozenges. Moreover, the entire population fared better without the use of antibiotics than would be predicted by national statistics.⁴ When zinc gluconate glycine lozenges were administered at the first sign of cold signs and/or symptoms, antibiotic use was not therapeutically required.

Safety

Unlike other studies,¹⁹ there were no adverse events reported by either subjects or medical staff when using zinc gluconate glycine lozenges as prophylaxis or treatment.

DISCUSSION

Results of this open-label prospective study indicate that once daily administration of zinc gluconate



* $p < 0.001$

FIGURE 2. The frequency distribution of cold duration with and without zinc gluconate glycine lozenges therapy is shown. The most frequently observed cold duration was 5 days with zinc gluconate glycine lozenges therapy, significantly shorter than the 11 days without zinc gluconate glycine lozenges therapy.

glycine lozenges to school-aged subjects provided significant prophylaxis against colds throughout the entire cold season. Study results also indicated that zinc gluconate glycine lozenges substantially contribute to the low incidence of antibiotic use in this population. As demonstrated, zinc gluconate glycine lozenges are easily administered, safe, and well tolerated by children.

The significant prophylaxis results in this study are consistent with results from several previous studies. Al-Nakib et al¹⁶ carried out a double-blind, placebo-controlled study to determine the prophylactic effect of zinc gluconate lozenges on rhinovirus challenge. Results of the study, which included 57 subjects, showed that 23-mg zinc gluconate lozenges administered every 2 hours while subjects were awake for 4.5 days beginning 1 day before virus inoculation reduced the total mean clinical score to 5.7 versus 8.2 for the placebo group.

The effectiveness of prophylaxis with zinc gluconate glycine lozenges in reducing the number of colds is particularly important, and it has been shown that more than 50 million colds in school-aged children

required medical attention in 1996,^{2,4} with a cost of annual productivity lost due to caring for children with colds that exceeded \$230 million.⁵

The current results confirm and extend those of our previous chart review, which showed that treatment with zinc gluconate glycine lozenges reduced cold duration.¹³ Results from that study also indicated that prophylactic administration of zinc gluconate glycine lozenges significantly reduced the median number of colds from 1.3 in untreated subjects to 0 per year ($P < 0.0001$). It should also be noted that the antibiotic use reported in the current study (0%) is in agreement with that found in the retrospective study (3%)¹³ for subjects using prophylactic zinc gluconate glycine lozenges. These results represent a dramatic reduction in antibiotic use at the Heritage Center. This represents significant financial savings as well as preventing antibiotics overuse, which contributes to antimicrobial resistance.

Taken together, the present prospective study and the prior retrospective study demonstrate the effectiveness of zinc gluconate glycine lozenges in more than 500 school-aged children.

Previous studies have provided mixed results regarding the therapeutic efficacy of zinc gluconate glycine lozenges. For example, Godfrey et al¹⁷ reported that treatment with zinc gluconate glycine lozenges shortened the time to symptom resolution from 6.1 to 4.9 days in 73 young adults during a placebo-controlled, double-blind study. Mossad et al¹⁸ reported that subjects treated with zinc gluconate glycine lozenges experienced complete symptom resolution in an average of 4.4 days versus 7.6 days for those taking placebo in a randomized, double-blind, placebo-controlled study that included 100 subjects who developed cold symptoms within 24 hours of study entry. Turner and Cetnarowski¹⁹ reported that in subjects with experimentally induced colds, treatment with zinc gluconate glycine lozenges resulted in a median duration of illness of 2.5 versus 3.5 days for those taking placebo. Prasad et al¹⁵ reported that administration of zinc acetate lozenges was associated with reduced duration and severity of cold symptoms in 50 individuals enrolled in a randomized, double-blind study.

In summary, the results of this prospective study indicate that the use of zinc gluconate glycine lozenges significantly reduces the risk of colds in school-aged subjects and supports the current National Center for Infectious Diseases (NCID) and Centers for Disease Control and Prevention (CDC) National Campaign for Appropriate Antibiotics Use in the Community.²⁰ Furthermore, the confirmation of the retrospective chart review and this prospective study, compared with national averages,⁴ suggests the appropriateness of administering Cold-Eeze to this population to reduce the number and duration of colds. Additionally, with no negative impact on school-aged children and in alignment with the CDC recommendations to reduce inappropriate use of antibiotics, Cold-Eeze zinc gluconate glycine lozenges are a positive and safe alternative for prevention and treatment of the common cold.

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