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RANDOMIZED, DOUBLE-MASKED, PLACEBO-CONTROLLED CLINICAL STUDY OF THE EFFECTIVENESS OF ZINC ACETATE LOZENGES ON COMMON COLD SYMPTOMS IN ALLERGY-TESTED SUBJECTS

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ABSTRACT

This report of a randomized, double-masked, placebo-controlled clinical study demonstrates the effectiveness of zinc acetate lozenges on common cold symptoms in allergy-tested subjects. Subjects in the zinc and placebo groups were evenly matched with respect to sex, race/ethnicity, allergy test status, and age. Overall symptom duration was significantly less in the zinc group than in the placebo group (mean, 3.8 days vs 5.1 days). The mean severity rating for all symptoms was lower in the zinc group than in the placebo group; this difference, however, was not statistically significant. Allergy-positive subjects who used zinc had a statistically significant shorter duration of nasal symptoms than allergy-negative subjects (3.5 days vs 7.6 days). In conclusion, we propose that zinc acetate lozenges may significantly shorten the duration of common cold symptoms and relieve symptoms associated with allergies. Key words: zinc acetate, common cold, allergies, lozenges.

INTRODUCTION

The common cold is the most frequent infection in all age groups in the United States.1 About $5.5 billion are spent annually on colds in the United States, yet only about 50% of the people with colds spend money treating them. It is estimated that in the United States more than 1 billion colds occur each year, of which 110 million are disabling; the result is about 300 million days of restricted activity, about 60 million lost days of school, and about 50 million lost days of work.2

Although it is well recognized that most colds are caused by rhinoviruses, at least $37.5 million worth of antibiotics were prescribed for the common cold in 1994 in the United States.3 This acute respiratory disorder

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can be induced by more than 200 types of viruses, mainly human rhinoviruses. Other cold viruses infect people at varying times of the year; they include coronavirus, influenza virus, herpes simplex virus, respiratory syncytial virus, coxsackievirus, parainfluenza virus, picornavirus, paramyxovirus, adenovirus, and echovirus. Viruses are usually contagious during the first 3 days of symptoms. Rhinoviruses, which can cause cold symptoms year-round, have been implicated in most cases. More than 100 distinct rhinoviruses exist, making it impossible to produce a useful vaccine. Recent literature offers little support for the use of antihistamines to treat symptoms of the common cold.

In 1974, it was reported that zinc ions inhibit rhinovirus replication. Since that observation, numerous studies have assessed the efficacy of zinc, given as oral lozenges, for the treatment of common cold symptoms. The effect of zinc lozenges on the duration of common cold symptoms has been inconsistent, perhaps due to different formulations of the zinc. In his Handbook for Curing the Common Cold, Eby discusses in great detail his understanding of how zinc ions work. It has been proposed that zinc ions interfere with rhinovirus protein cleavage, protect plasma membranes, attach to the surface of the rhinovirus, and interfere with the intercellular adhesion molecule 1 (ICAM-1), the docking point for rhinoviruses on the surface of nasal epithelial cells. In 1984, Eby et al conducted the first clinical trial using zinc gluconate lozenges and demonstrated that zinc shortened the duration of common cold symptoms. The second clinical trial, conducted by the Medical Research Council Common Cold Unit in Salisbury, England, also demonstrated a shorter duration of common cold symptoms when zinc lozenges were used. A recent randomized, double-masked, placebo-controlled study of zinc lozenges at The Cleveland Clinic demonstrated a significantly reduced duration of symptoms of the common cold. Some clinical studies, however, showed no improvement in cold symptoms when zinc lozenges were used.

A recent review of published clinical studies on the use of zinc lozenges in colds found four studies that reported zinc salts to be beneficial and four that did not; the reviewers concluded that evidence is still lacking. However, they also stated that the four studies that did not show benefits used zinc lozenges with substances known to complex zinc ions, whereas the four studies with positive results used an ionizable form of zinc without such substances.

A recent study evaluated the effects of zinc gluconate glycine lozenges on cold symptoms in children and adolescents. The results showed no advantage to using zinc lozenges; however, the authors admitted that the dose of zinc may have been too low and that the cherry flavoring may have inactivated the zinc. Thus an ineffective formulation may have biased the study.
The present study was undertaken to test the effectiveness of zinc acetate lozenges on common cold symptoms because the results of past clinical investigations have been interpreted as inconclusive, formulations of the zinc lozenges were not identical, the placebos used resulted in inadequate masking, and the presence of allergies that present as common cold symptoms were not addressed.

SUBJECTS AND METHODS

The subjects of this randomized, double-masked, placebo-controlled study were 102 volunteers recruited from the campus of the University of Texas at Austin through posted announcements. A goal of 100 volunteers was planned because a power analysis showed that 49 subjects per group are needed to detect a moderate effect size (ES = 0.5) with 80% power and alpha = 0.05 (one-tailed). Subjects were 18 to 54 years of age (mean age, 26.5 years; median age, 22 years) and were healthy except for common cold symptoms. All subjects signed an informed consent form approved by an institutional review board. Patient diaries were completed by 101 subjects; 1 subject was lost to follow-up.

The zinc treatment group consisted of 52 subjects (51.5%), and the placebo group consisted of 49 subjects (48.5%). Each subject was given a bottle of 180 lozenges. The lozenges with zinc contained 9 mg of zinc in a 2.7-g dextrose base.

Subjects with serious illnesses, organ transplants, or disability (including human immunodeficiency virus infection) were excluded from the study. Subjects were instructed not to use antihistamines, decongestants, aspirin, or vitamin supplements. None of the subjects had a history of alcohol or drug abuse, and none had participated in an investigational drug study within the preceding 30 days. Physical examinations were within acceptable limits, and all women had a negative result on a urine pregnancy test.

Because common colds and nasal allergies cause many of the same symptoms, skin tests were performed on each subject to determine whether allergies were present. All subjects were skin tested with 20 different allergy extracts, using a Duotip-Test® applicator (Lincoln Diagnostics, Inc., Decatur, Illinois) on both lower forearms. The allergy extracts were obtained from Allergy Laboratories of Ohio (Columbus, Ohio). The extracts included ragweed mix, burweed marsh elder, cedar elm, Bermuda grass, Johnson grass, perennial rye grass, mountain cedar (juniper), Virginia live oak, pecan, American elm, Alternaria alternata, Hormodendrum cladosporioides, Helminthosporium sativum, cockroach mix (American and German), cat dander, dog dander, dust mite mix, Western ragweed, a negative control (diluent), and a positive control (histamine). After a 15- to 30-minute waiting period, the results of the skin test were measured and recorded. Itching, swelling, or redness at the site of allergy extract appli-
cation indicated a positive reaction to the allergen. Forty-six subjects (46%) tested positive for allergies, and 55 (54%) were negative.

This study was conducted during July and August 1997, when pollen was at its lowest level. Airborne pollen and spore counts were high for mold spores (726–2676) and scant for grasses (8–16) during the study. Of the 46 subjects who had positive skin test results, 4 were allergic to molds and 21 were allergic to grasses. From a practical viewpoint, airborne pollen was not a significant factor in the study.

To be eligible for this study, subjects had to have two or more common cold symptoms (nasal drainage, nasal congestion, cough, fever, myalgia, headache, sore throat, scratchy throat, hoarseness, sneezing, or malaise) and had to be willing to use lozenges for 14 days or until symptoms stopped. Because this was a randomized, double-masked study, subjects were informed that some individuals would receive zinc lozenges and some would receive placebo. Subjects were also informed that they were required to rate and record their symptoms in a diary at the same time each day. Symptoms were graded as follows: 0 = absent; 1 = mild (symptom is present but not particularly a discomfort); 2 = moderate (symptom is clearly evident and a discomfort); or 3 = severe (symptom is a serious problem and clearly evident and a discomfort). Subjects were instructed to use a lozenge every 1.5 hours while awake during day 0, then one lozenge every 2 hours while awake on following days while symptoms were present. They stopped taking lozenges 6 hours after the symptoms stopped. Subjects recorded their symptoms every day until their symptoms ceased; this was considered the day their involvement in the study ended. Subjects were interviewed regarding the accuracy of their diary entries at their last visit and were compensated $100 for participating in the study.

**Statistical Analysis**

Chi-square tests were used to determine whether subjects in the zinc and placebo groups were evenly distributed with respect to sex, race/ethnicity, and allergy test status. Independent groups t tests were used to test for differences between the zinc and placebo groups in mean age, mean number of days with symptoms, and mean symptom severity ratings.

Although distributions of the outcome variables departed slightly to moderately from normal, parametric tests were used because even severe departures from normality make little practical difference in the conclusions reached as long as the sample size is at least moderate. To control for subjects' allergy test status, two-way analysis of variance (ANOVA) procedures were used to determine whether the mean number of days with symptoms or mean symptom severity ratings differed with respect to treatment group and allergy test status considered simultaneously. Data analyses were conducted using SPSS version 7.5.
Values are given in the Results as the mean ± the standard error of the mean (SEM).

RESULTS

Table I shows the distribution of subjects by treatment group for sex, race/ethnicity, and allergy test status. The study group was predominantly white (72%) with relatively even distributions by sex and allergy test status. Chi-square tests showed no significant associations between treatment group membership and sex, race/ethnicity, and allergy test status. An independent groups t test showed no significant difference in mean age between the zinc group (26.7 ± 1.3 years) and the placebo group (26.3 ± 1.2 years) (t = 0.197, df = 99, P = 0.844).

Only 1 subject was lost to follow-up, and none of the remaining 101 subjects discontinued because of side effects from the lozenges. A mean total of 60.4 lozenges were taken by each subject for the study, which averaged 9.9 lozenges per subject per day as long as symptoms persisted.

To achieve masking, sucrose octaacetate (0.169 mg) was used in the placebo, and both the placebo and zinc lozenges were peppermint flavored. A review of subjects' diary entries revealed that 4 subjects noted a chalky taste, 4 experienced a metallic aftertaste, and 3 complained of an upset stomach; none of the subjects noted a bitter taste. Most subjects liked the peppermint flavor.

Table II shows the mean duration of all symptoms (duration of each symptom + number of symptoms), the mean duration of the longest-lasting symptom (symptom with the longest duration), and the mean severity

| Table I. Distribution of subjects by treatment group for selected variables. |
|-------------------|---|---|---|---|---|---|---|
|                  | Overall | Zinc | Placebo | Chi-square* | df | P  |
| Variable     | n | % | n | % | n | % |  |
| Sex          |   |   |   |   |   |   |   |
| Male         | 47 | 47 | 25 | 48 | 22 | 45 | 0.10 | 1 | 0.75 |
| Female       | 54 | 53 | 27 | 52 | 27 | 55 | 0.07† | 1 | 0.83 |
| Race/ethnicity |   |   |   |   |   |   |   |
| White        | 73 | 72 | 37 | 71 | 36 | 73 | 0.07† | 1 | 0.83 |
| Hispanic     | 10 | 10 | 6  | 12 | 4  | 8  |       |   |     |
| Black        | 15 | 15 | 9  | 17 | 6  | 12 |       |   |     |
| Asian        | 3  | 3  | 0  | 0  | 3  | 6  |       |   |     |
| Allergy test status |   |   |   |   |   |   |   |
| Positive     | 46 | 46 | 23 | 44 | 23 | 47 | 0.08 | 1 | 0.79 |
| Negative     | 55 | 54 | 29 | 56 | 26 | 53 |       |   |     |

* Chi-square tests were conducted to determine if treatment group membership was independent of group membership for the variables listed.
† Because of low cell frequencies, race/ethnicity categories were collapsed into white and nonwhite for this analysis.
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rating (a mean score for all symptoms) by treatment group. An independent groups t test showed that the mean duration of all symptoms was significantly lower in the zinc group (3.8 ± 0.2 days) than in the placebo group (5.1 ± 0.4 days) \((P = 0.008)\) (Figure 1). The mean duration of the longest-lasting symptom was also significantly lower in the zinc group (5.3 ± 0.4 days) than in the placebo group (7.1 ± 0.6 days) \((P = 0.009)\) (Figure 2). The mean severity rating (for all symptoms) was lower in the zinc group (1.41 ± 0.04) SEM than in the placebo group (1.50 ± 0.04); however, this difference was not statistically significant. When symptoms were present, they were generally rated as mild or moderate.

Table III shows the mean duration of each symptom by treatment group. An independent groups t test showed that the mean duration of nasal drainage symptoms was significantly lower in the zinc group (4.2 ± 0.4 days) than in the placebo group (6.6 ± 0.7 days) \((t =-3.1, df = 75, P = 0.003)\). A t test also showed that the mean duration of nasal congestion symptoms was significantly lower in the zinc group (4.2 ± 0.4 days) than in the placebo group (6.5 ± 0.7 days) \((t =-2.8, df = 71, P = 0.006)\). None of the other mean durations (for symptoms considered individually) were significantly different between treatment groups.

Table III also shows the mean severity ratings for each symptom by treatment group. The mean symptom severity ratings were lower in the zinc group than in the placebo group for 9 of the 11 symptoms; however, none of the differences were statistically significant. Mean symptom ratings ranged between mild and moderate.

ANOVA procedures were used to determine whether the number of days of symptoms or the symptom severity ratings differed with respect to treatment group and allergy test status considered simultaneously. The mean duration of nasal drainage symptoms by treatment group and al-

| Table II. Mean duration and mean severity of symptoms by treatment group. Values are given as mean (SEM). |
|---------------------------------------------------------------|
| Variable | Overall (n = 101) Mean (SEM) | Zinc (n = 52) Mean (SEM) | Placebo (n = 49) Mean (SEM) | t test* | df | P |
|----------------------------------|-----------------|-----------------|-----------------|-------|---|---|
| Duration of all cold symptoms (days) | 4.4 (0.2) | 3.8 (0.2) | 5.1 (0.4) | -2.7 | 73.8† | 0.008 |
| Duration of longest-lasting cold symptom (days) | 6.1 (0.3) | 5.3 (0.4) | 7.1 (0.6) | -2.7 | 82.2† | 0.009 |
| Mean severity rating† (all symptoms) | 1.45 (0.03) | 1.41 (0.04) | 1.50 (0.04) | -1.4 | 99 | 0.161 |

SEM = standard error of the mean.
* Independent groups t tests were used to determine whether differences existed between the zinc and placebo group means.
† Results using estimates assuming unequal group variances.
‡ Symptom severity rating scale: 0 = absent; 1 = mild; 2 = moderate; and 3 = severe.
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Figure 1. The mean (± standard error of the mean) duration of all cold symptoms reported by subjects was significantly lower in the zinc group (3.8 ± 0.2 days) than in the placebo group (5.1 ± 0.4 days) (P = 0.008).

The duration of nasal drainage symptoms was significantly lower in the zinc group (4.2 ± 0.4 days, n = 39) than in the placebo group (6.6 ± 0.7 days, n = 38) (F = 10.3; df = 1, 73; P = 0.002). However, ANOVA also showed a significant interaction effect between treatment group and allergy status group (F = 4.5; df = 1, 73; P = 0.037). This difference was even more pronounced in allergy-positive subjects (3.5 ± 0.5 days in the zinc group vs 7.6 ± 1.1 days in the placebo group) than in allergy-negative subjects (4.7 ± 0.5 days in the zinc group vs 5.5 ± 0.8 days in the placebo group). This finding suggests that persons positive for allergies are more responsive to zinc than allergy-negative persons for relief of nasal drainage symptoms. ANOVA showed no significant differences for any of the symptoms, regardless of the number of days the symptoms existed before entering the study, between treatment groups and allergy status groups.

DISCUSSION

The results of this randomized, double-masked, placebo-controlled study suggested that using zinc acetate lozenges significantly reduced the duration of common cold symptoms. This study, although descriptive, also demonstrated that all symptoms resolved significantly more quickly in the zinc group than in the placebo group. The mean severity rating was lower in the
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Figure 2. The mean (±standard error of the mean) duration of the longest-lasting cold symptom reported by subjects was significantly lower in the zinc group (5.3 ± 0.4 days) than in the placebo group (7.1 ± 0.6 days) (P = 0.009).

Eby explained the differing results in previous clinical trials as due to variations in zinc ion availability, noting that only positively charged zinc ions can shorten the duration of common cold symptoms. Only those studies that used zinc lozenges that released positively charged zinc ions at physiologic pH demonstrated impressive, beneficial results. The lozenges used in this study contained 9 mg of zinc in a tablet base of agglomerated dextrose and no other water-soluble ingredients, and they dissolved in the mouth in about 15 minutes. Hatch and Berthon found that zinc acetate releases essentially 100% of its zinc as Zn$^{2+}$ ions at physiologic pH and lower.

Zinc is an essential trace element in human biology necessary for many biologic functions such as growth, appetite, testicular maturation, skin integrity, mental activity, wound healing, and immune system maintenance. Approximately 300 enzymes are known to require zinc for their activities. Zinc deficiency in humans is widespread and more prevalent in areas where the population subsists on cereal proteins. Clinical manifestations of zinc deficiency include growth retardation, hypogonadism in males, neurosensory disorders, cell-mediated immunologic dysfunctions, increased maternal morbidity, and premature delivery. Zinc deficiency also adversely affects the proliferation, regulation, and maturity of lymphocytes.
Table III. Mean duration and mean severity rating of each cold symptom by treatment group.

| Symptom          | Mean Duration of Symptoms | Mean Severity Rating* |
|------------------|---------------------------|-----------------------|
|                  | Overall Mean Days (SEM)   | Zinc Mean Days (SEM)  |
|                  |                           | Placebo Mean Days (SEM) | Overall Mean Rating (SEM) | Zinc Mean Rating (SEM) | Placebo Mean Rating (SEM) |
| Headache         | 4.2 (0.4)                 | 4.4 (0.4)             | 4.0 (0.6)               | 1.48 (0.06)            | 1.43 (0.07)               | 1.52 (0.10)               |
| Fever            | 2.1 (0.5)                 | 1.8 (0.5)             | 2.5 (0.9)               | 1.13 (0.08)            | 1.00 (0.09)               | 1.25 (0.14)               |
| Myalgia          | 4.1 (0.5)                 | 4.6 (0.5)             | 3.9 (0.9)               | 1.48 (0.09)            | 1.37 (0.15)               | 1.51 (0.11)               |
| Sneezing         | 4.7 (0.5)                 | 3.9 (1.1)             | 5.5 (0.6)               | 1.34 (0.06)            | 1.31 (0.06)               | 1.38 (0.07)               |
| Nasal drainage   | 5.4 (0.4)                 | 4.2 (0.4)             | 6.0 (0.8)               | 1.53 (0.06)            | 1.45 (0.07)               | 1.51 (0.07)               |
| Nasal congestion | 5.4 (0.4)                 | 4.2 (0.4)             | 6.5 (0.7)               | 1.49 (0.05)            | 1.54 (0.08)               | 1.43 (0.06)               |
| Sore throat      | 3.4 (0.3)                 | 3.4 (0.4)             | 3.3 (0.7)               | 1.29 (0.05)            | 1.26 (0.08)               | 1.34 (0.06)               |
| Scratchy throat  | 4.3 (0.3)                 | 4.0 (0.4)             | 4.5 (0.5)               | 1.47 (0.06)            | 1.38 (0.06)               | 1.53 (0.10)               |
| Cough            | 4.4 (0.4)                 | 4.5 (0.5)             | 4.3 (0.4)               | 1.39 (0.06)            | 1.28 (0.07)               | 1.51 (0.09)               |
| Hoarseness       | 3.8 (0.6)                 | 2.7 (0.5)             | 4.7 (0.9)               | 1.39 (0.09)            | 1.35 (0.12)               | 1.43 (0.14)               |
| Malaise          | 5.2 (0.7)                 | 5.7 (0.7)             | 5.0 (0.9)               | 1.50 (0.06)            | 1.50 (0.09)               | 1.50 (0.08)               |

SEM = standard error of the mean.
* Symptom severity rating scale: 0 = absent; 1 = mild; 2 = moderate; and 3 = severe.
† t test results: $t = -3.1, df = 75, P = 0.003$.
‡ t test results: $t = -2.8, df = 71, P = 0.006$.

The relationship of zinc and the common cold has been well reviewed. Most colds are caused by rhinoviruses. Korant et al determined that zinc ions inhibit rhinoviral replication and the cleavage of rhinovirus polypeptides. Rhinoviruses have been found to bind with ICAM-1, a receptor found on nasal epithelium. It has been proposed that zinc ions complex with ICAM-1-binding sites and prevent the rhinovirus from attaching to the nasal tissue, a point briefly mentioned by Korant et al in 1974. If zinc-blocked viruses do not infect nasal tissue cells to replicate, the infectious process would be interrupted and the duration of the cold would be markedly shortened. Zinc is also believed to act as a protease inhibitor in its effect against rhinovirus infections. Other common cold-causing viruses inhibited by zinc ions include herpes simplex virus and coxsackievirus.

Zinc ions have other benefits that may shorten the severity and duration of nonviral symptoms associated with the common cold. Zinc has antibacterial activity. It can inhibit the growth of streptococci and actinomycetes when used as a dentifrice. Zinc compounds have antiseptic, antifungal, and astringent properties. As an astringent, zinc can be used...
Table IV. Mean duration of nasal drainage symptoms by treatment group and allergy test status.

| Group                  | Zinc Mean Days (SEM) | Placebo Mean Days (SEM) | Overall Mean Days (SEM) |
|------------------------|----------------------|-------------------------|-------------------------|
|                       |                      |                         |                         |
| Allergy positive       | 3.5* (0.5)           | 7.6* (1.1)              | 5.7 (0.7)               |
| n = 17                 | n = 19               | n = 36                  |
| Allergy negative       | 4.7* (0.5)           | 5.5* (0.8)              | 5.1 (0.5)               |
| n = 22                 | n = 19               | n = 41                  |
| Total                  | 4.2† (0.4)           | 6.6† (0.7)              | 5.4 (0.4)               |
| n = 39                 | n = 38               | n = 77                  |

SEM = standard error of the mean.

Per analysis of variance.

Interaction effect: F = 4.5; df = 1, 73; P = 0.037.

† Main effect for treatment group: F = 10.3; df = 1, 73; P = 0.002.

therapeutically to arrest hemorrhage by coagulating blood, check diarrhea, reduce inflammation of mucous membranes, promote healing, toughen skin, and decrease sweating. Zinc’s dominant biological action is membrane stabilization.

Zinc is an essential element in immune system function. With regard to the effect of zinc on allergies, mast cells have been implicated as mediators of type I allergic reactions and common cold symptoms by causing tissue redness, inflammation, nasal congestion, release of mucus from goblet cells, nose and throat pain, tickling and itchiness, and, indirectly, coughing and sneezing. Mast cell–derived reactions result when histamine, heparin, prostaglandins, slow-reacting substance of anaphylaxis, and various vasoactive amines are released from granules on the surface of mast cells, possibly including kinins. One product of mast cell–induced inflammation in response to rhinoviral infection is fever. The inhibitory effect of zinc on histamine release from mast cells is attributed to its action on the stabilization of mast cell membrane. Zinc ions were found to stabilize cell plasma membranes and prevent induced histamine and vasoactive amine release from tissue mast cells. It has been observed that unsequestered zinc ions (4 to 20 mM) are released from mast cell granules during inflammation, suggesting a common linkage between allergies and common colds. Marone et al believed that zinc is a competitive antagonist of histamine release from human basophils, and they suggested that zinc compounds might be considered for the treatment of allergic disorders. Pasternak proposed that cell membrane stabilization by Zn was the likely mechanism of action in the treatment of common colds with lozenges releasing positively charged zinc ions.
The purpose of our study was to subjectively evaluate the effects of zinc acetate lozenges on the duration and severity of common cold symptoms, not verify the antiviral effect of zinc as previously published. Our study found that zinc acetate lozenges significantly reduced the duration of common cold symptoms and that zinc acetate lozenges were most effective in reducing the duration of nasal drainage symptoms in allergy-positive subjects. We hypothesize that zinc lozenges may be useful as a first line of treatment for allergy symptoms, and we recommend additional research on the use of zinc in allergy therapy.

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