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# Failure of Zinc Gluconate in Treatment of Acute Upper Respiratory Tract Infections

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**Zinc is a trace metal with in vitro activity against rhinovirus, the major etiologic agent in acute upper respiratory tract infections (URIs). A previous trial of zinc gluconate supported its efficacy in treating URIs, but the effectiveness of blinding was uncertain. We conducted a prospective randomized trial of zinc gluconate versus a taste-matched placebo of sucrose octaacetate. Lozenges containing either 23 mg of elemental zinc or placebo were taken every 2 h. Eleven URI symptoms were rated daily on a scale of 0 (not present) to 3 (severe). Duration of illness, reflected in the proportion of subjects remaining symptomatic on each day, was not significantly reduced (maximum difference of 12.6% on day 7, $P = 0.09$; 95% confidence interval, −6 to 31%) by either treatment. Severity of illness, assessed by using a summed severity score, was reduced incrementally by 7 to 8% on days 5 to 7 ($P = 0.02$) in subjects taking zinc. Adverse effects, mostly nausea and altered taste, were reported by 50% of subjects taking zinc. We conclude that while zinc gluconate may produce a small reduction in overall severity of symptoms, this is not clinically significant. Given the additional high incidence of adverse effects, zinc gluconate cannot be recommended for use in the treatment of acute URIs.**

Rhinovirus is the principal causative agent in acute upper respiratory tract infections (URIs) (6). Although alpha 2 interferon has been demonstrated to have prophylactic efficacy in rhinoviral colds (7), no effective antiviral drug is available to treat the symptomatic illness. Zinc ions have been found to reversibly inhibit rhinovirus replication in vitro, possibly by complexing with capsid proteins, preventing them from acting as substrates for proteases (8). In a previous randomized clinical trial (3), zinc gluconate in a lozenge form was reported to reduce the mean duration of URIs by about 4 days and to significantly reduce the severity of symptoms. The taste of zinc gluconate is quite distinctive, however, and we were concerned that the effectiveness of blinding in the initial trial might have been compromised. We therefore conducted a prospective randomized double-blinded trial of zinc gluconate in naturally acquired URI, using a protocol identical to that in the previous study, but in addition used a taste-matched placebo of sucrose octaacetate.

## MATERIALS AND METHODS

**Study population.** Subjects were recruited from among the students of three colleges and from one family practice during January to May 1986. All eligible subjects had a clinical diagnosis of acute URI. No viral cultures were taken.

Potential subjects were excluded from the study if they had serious acute or chronic medical conditions, seasonal allergies, productive cough, or indication for antibiotic therapy or had taken treatment for symptoms within 8 h of the baseline evaluation. All those enrolled were over 18 years old and gave written informed consent. Subjects were informed of the positive outcome of the initial study and were told that the purpose of the present study was to confirm this result.

**Medication and randomization.** Identical-appearing lozenges containing either 11.5 mg of elemental zinc or sucrose octaacetate were used. The latter was chosen because its taste empirically approximated that of zinc gluconate. Upon enrollment, subjects were randomly assigned to receive either zinc gluconate or placebo. Both subjects and investigators were blinded to treatment.

An initial dose of four lozenges was used, followed by two lozenges dissolved in the mouth every 2 h while awake. This course was continued for 7 days or 24 h after the disappearance of the last symptom. Subjects were not allowed to use additional cold or analgesic preparations. Compliance was assessed through daily estimates by the subjects of the number of lozenges consumed and pill counts by the investigators.

In order to assess the efficacy of blinding, a subsample of 40 subjects were asked at the conclusion of the trial to indicate whether they had been taking zinc or placebo. Their responses were compared with their actual assignments by a chi-square test of significance.

**Illness surveillance and toxicity monitoring.** Upon enrollment and at the end of each study day, subjects rated the severity of 11 symptoms and the overall severity of their URI on a scale of 0 to 3 (absent to severe). The individual symptoms assessed were sneezing, runny nose, stopped-up nose, sore or scratchy throat, hoarseness, postnasal drip, cough, watery eyes, headache, chilliness, and muscle aches. Any potential adverse effects were recorded daily. All 170 subjects enrolled, including dropouts, were surveyed for toxic effects.

**Assessment of efficacy.** The effect of treatment on duration of illness was assessed by comparing the proportion of subjects reporting symptoms on each day of the trial. The

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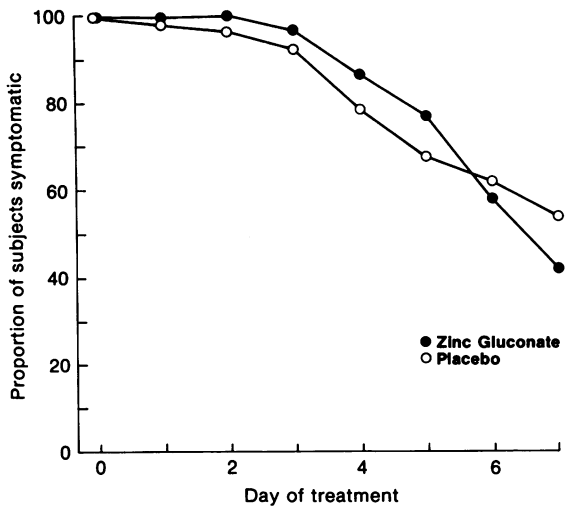


FIG. 1. Effect of zinc gluconate on duration of URI.

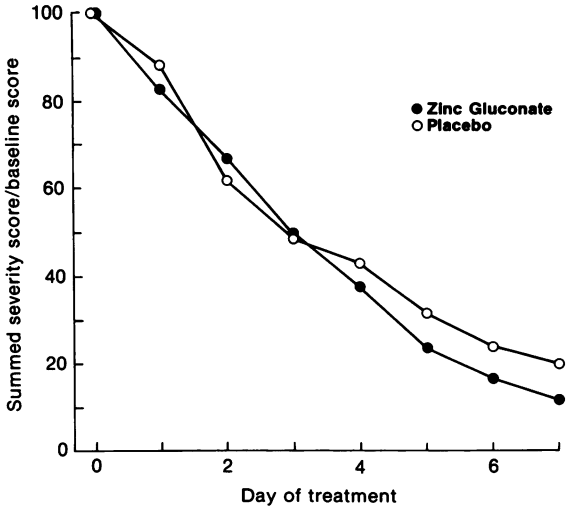


FIG. 2. Effect of zinc gluconate on severity of URI.

effect on severity of illness was assessed by comparing changes from the baseline in the summed severity score (sum of the individual ratings for each symptom) on each day. Subjects were excluded from analysis for insufficient dose (less than 10 lozenges on any day) or duration of therapy and for loss to follow-up. All comparisons were made with a two-way analysis of variance in order to be sensitive to significant improvements occurring only early or later in therapy. Confidence intervals were calculated for differences in response rates (9).

## RESULTS

**Study population.** Of 174 eligible subjects with a clinical diagnosis of acute URI, 88 were assigned to receive placebo and 86 were assigned to receive zinc gluconate. Thirty-five subjects in the placebo group and 29 taking zinc were excluded from analysis for reasons of insufficient dose or duration of therapy. Only two in each group were lost to follow-up. The remaining groups of 53 subjects taking placebo and 57 taking zinc did not differ with respect to age, sex, initial severity score, number of symptoms, or duration of symptoms.

**Effect on duration and severity of illness.** The duration of illness, reflected in the proportion of subjects who continued to have symptoms on each day of treatment, was not affected by zinc gluconate. Response to zinc did not become directionally superior to placebo until the sixth study day (Fig. 1), and the maximal difference of 12.6% seen on day 7 was not statistically significant ($P = 0.09$; 95% confidence interval, −6 to 31.2% difference).

The severity of illness is reflected in the sum of the individual symptom severity scores on any day as a proportion of the baseline score. Subjects taking zinc gluconate had lower severity scores than those in the corresponding placebo group on days 4 to 7 of treatment (Fig. 2). This difference is statistically significant ($P = 0.02$; 95% confidence interval, 1 to 16% difference); however, the incremental improvement in severity score of 7 to 8% is small in clinical terms.

Adjustments in analysis for dosage taken or delay in initiation of treatment from the onset of symptoms did not alter these findings.

**Adverse effects of medication.** Adverse effects of treatment, mostly minor, were reported by 50% of subjects taking zinc gluconate (Table 1).

**Adequacy of blinding.** In a comparison of which compound the subjects guessed they had received with the actual assignment, 19 subjects (47%) correctly identified whether they were on zinc gluconate or placebo, while the other 53% were either incorrect or uncertain. Of those given zinc gluconate, 57% identified it correctly, while 32% of subjects given placebo incorrectly thought it was zinc. The ability to discriminate between zinc gluconate and sucrose octaacetate was not significant ($P = 0.24$).

## DISCUSSION

We found that zinc gluconate, when used to treat naturally acquired acute URIs, produced a minor reduction in the overall severity of symptoms late in the course of therapy and had no effect on the duration of symptoms. These findings stand in sharp contrast to those reported in an earlier clinical trial with a parallel design (Eby et al. [3]). In their study, zinc gluconate was significantly more effective in reducing the severity and duration of symptoms, beginning on the first day of treatment.

While our study was designed to replicate the previous trial and so used identical doses of zinc gluconate and identical outcome measures, there were important differences which might explain the disparity in findings. The first is the element of blinding. The Eby et al. trial used an unflavored placebo, while zinc gluconate has a strong metallic taste. That subjects were able to discern a difference is

TABLE 1. Adverse effects of treatment

| Adverse effect | % of subjects | |
|---|---|---|
| | Zinc | Placebo |
| Nausea | 24 | 16 |
| Altered taste | 11 | 3 |
| Dry mouth | 15 | 6 |
| Abdominal pain/dyspepsia | 5 | 0 |
| Headache | 6 | 2 |
| Dizziness | 0 | 5 |
| Weakness | 0 | 4 |
| Constipation | 1 | 1 |

suggested by the high dropout rate (30%) in the zinc group in that study, nearly double that in the placebo group. We formulated a placebo which empirically matched the zinc gluconate in taste. Our success in blinding is supported by the inability of subjects in our trial to distinguish between the zinc and placebo and by a dropout rate attributable to unpalatability that was equal in both the zinc and placebo groups (and equal to that of the zinc group in the Eby et al. study). The slight trend in this study in favor of identification of zinc, even if significant, would have produced a bias in favor of the zinc treatment. The positive effect on outcome in the earlier study when blinding was not addressed is reminiscent of the misleading early reports of the efficacy of ascorbic acid in treatment of the common cold (1).

A second difference between the studies was the time of year during which each study was conducted. The Eby et al. trial accrued patients during the fall, while our study was run during the spring. The viral agents causing the illnesses were not confirmed in either study. It is possible that etiology in the two populations differed markedly, but rhinovirus has seasonal peaks in both the spring and fall (5) and is the predominant etiologic agent in URIs in adults. In addition, since viral cultures are not generally used in the diagnosis of acute URI, the etiologic agents in our study sample are likely to be similar to those in a population in which zinc would be used based on clinical diagnosis.

While our findings do not agree with those of Eby et al., they do correspond with those of two subsequent studies. Farr and associates (4) administered zinc gluconate lozenges to subjects with experimentally induced rhinovirus infections. They were unable to demonstrate an effect of zinc on the severity or duration of cold symptoms, the frequency or duration of viral shedding, or viral titers. Nasal mucous weights and number of tissues used were higher in subjects taking zinc gluconate. Douglas et al. (2) used effervescent zinc acetate lozenges in subjects with naturally acquired URIs. There were no differences in effect on severity or duration of symptoms between zinc and placebo recipients. The mean duration of symptoms was 4.4 days longer in subjects taking zinc acetate. Both of these studies were limited, however, by having too few subjects to eliminate the possibility of a type II error. Our study had nearly twice as many subjects as the Eby et al. trial, with more than adequate power to detect the magnitude of differences that they reported.

We conclude that in a carefully blinded trial, zinc gluconate lozenges are not superior to placebo in the treatment of naturally acquired acute URIs.

## ACKNOWLEDGMENTS

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