ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 1984, p. 20–24
0066-4804/84/010020-05$02.00/0

Vol. 25, No. 1

Reduction in Duration of Common Colds by Zinc Gluconate Lozenges in a Double-Blind Study

GEORGE A. EBY,[1]* DONALD R. DAVIS,[2] AND WILLIAM W. HALCOMB[3]

George Eby Research, Austin, Texas 78704[1]; Clayton Foundation Biochemical Institute, University of Texas at Austin, Austin, Texas 78712[2]; and 8311 Shoal Creek Boulevard, Austin, Texas 78756[3]

Received 19 April 1983/Accepted 17 October 1983

As a possible treatment for common colds, we tested zinc gluconate lozenges in a double-blind, placebo-controlled, clinical trial. One 23-mg zinc lozenge or matched placebo was dissolved in the mouth every 2 wakeful h after an initial double dose. After 7 days, 86% of 37 zinc-treated subjects were asymptomatic, compared with only 46% of 28 placebo-treated subjects ($P = 0.0005$). Side effects or complaints were usually minor and consisted mainly of objectionable taste and mouth irritation. Zinc lozenges shortened the average duration of common colds by about 7 days.

Since one-half or more of all acute illness in humans is caused by viral respiratory diseases, of which the common cold is a major component (12), an effective and safe treatment for common colds is greatly needed. A new approach to this problem was suggested by serendipitous observation by one of us (G.A.E.) in an immunosuppressed, 3-year-old girl undergoing chemotherapy for acute lymphocytic leukemia. Zinc was being administered in an effort to improve zinc status (2) and to stimulate T-cell lymphocyte responsiveness (23). The child also suffered from frequent and severe colds before and after diagnosis of leukemia. At the onset of one cold, she refused to swallow a 50-mg zinc (gluconate) tablet and dissolved it in her mouth instead. Within several hours her cold disappeared without further treatment. This unexpected response to zinc lozenges seemed to be reproducible in that child, as well as in many other children and adults.

A search of the literature revealed that zinc ions inhibit the replication of diverse viruses in vitro by inhibition of viral polypeptide cleavage. Among these viruses are eight of nine rhinoviruses tested and also herpes simplex viruses that are known to cause common colds (4, 5, 9, 10, 13, 14). After further explorations, we decided to carry out a double-blind, placebo-controlled trial to test the hypothesis that zinc gluconate lozenges may be clinically useful in the treatment of common colds.

MATERIALS AND METHODS

During the fall of 1981, the local media were used to invite persons with colds to volunteer for this experiment. All were accepted who were diagnosed by the physician (W.W.H.) to have signs and symptoms of the common cold. No limitation on the length of illness was imposed to encourage accurate reporting of length of illness. Informed consent was obtained in writing after explanation of the study and possible side effects.

We used unflavored zinc gluconate tablets commonly available over-the-counter as nutritional supplements, with matching placebos. Tablets contained 23 mg of zinc or 50 mg of calcium lactate. Both tablets were manufactured by Truett Laboratories of Dallas, Tex., and were otherwise identical, including excipients of dicalcium phosphate, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and FD&C yellow no. 5 and blue no. 1 (aluminum lake). A 7-day supply of tablets (active or placebo) was given to each subject, using a double-blind, random method.

The initial (loading) dose for all subjects was two tablets, one followed by the other, dissolved in the mouth as lozenges (about 10 to 20 min each). Thereafter, adults and youths dissolved one tablet every 2 wakeful h, not exceeding 12 and 9 tablets per day, respectively. Children under 60 pounds (27 kg) received one-half tablet every 2 wakeful h, not exceeding six tablets per day. Subjects were instructed to treat their cold until all symptoms had been absent for 6 h and then to stop all treatment. They were instructed to treat the cold during the night only if they were already awake. Other common cold treatments were not permitted. Emphasis was placed on the necessity of dissolving the tablets in the mouth as lozenges.

Subjects recorded the presence and severity of 10 common cold symptoms on a report form. Headache, fever, muscle pain, sneezing, nasal drainage, nasal obstruction, sore throat, scratchy throat, cough, and hoarseness were scored at specific times during the first day and at the same time of day as the initial treatment during the following 6 days. Symptoms were scored as being severe (3 points), moderate (2 points), minor (1 point), or absent (no points). Subjects also recorded side effects or complaints and any deviation from the protocol. Reports were returned by mail or in person to the physician.

Chi-square or *t*-test statistical tests were used throughout except as noted. *P* values below 0.05 were considered significant.

RESULTS

Of 146 (83 zinc, 63 placebo) original volunteers, 120 subjects returned reports. Initially, to use as much of the data as possible, we analyzed the 80 complete reports from 108 subjects who had been ill for 10 days or less at the start of treatment. After the 7-day experiment, 90% of these zinc-treated subjects reported no symptoms, compared with only 49% of the placebo subjects ($P < 0.0001$). However, this choice of subjects raised concerns about superimposed allergies or bacterial infections and about a disproportionate number of dropouts from the zinc group; also, it did not fully reflect our goal of a treatment for early colds.

Consequently, this report is restricted to those 65 subjects who reported being ill for 3 days or less before starting the

* Corresponding author.

TABLE 1. Characteristics of study group

Characteristic	Zinc	Placebo
Total subjects	37	28
Male/female	21/16	14/14
Age range (yr)	11–63	14–62
Mean age ± SEM (yr)	35.6 ± 2.2	38.0 ± 2.8
Smokers	10	7
History of any allergy	14	11
History of >4 colds per yr	5	6
History of use of zinc dietary supplements	4	3
History of use of vitamin C dietary supplements	12	10
Pretreatment duration of colds		
Mean (days ± SEM)	1.6 ± 0.2	1.6 ± 0.2
Median (days)	1.0	1.0
Range (days)	0.17–3.0	0.25–3.0
Initial total severity score		
Mean (points ± SEM)	8.7 ± 0.7	10.5 ± 0.7
Median (points)	8.0	10.0
Range (points)	3–20	4–18
Initial symptoms		
Mean (no. ± SEM)	5.2 ± 0.3	6.4 ± 0.4
Median (no.)	5	7
Range (no.)	3–10	2–9

experiment. The results are similar, but (as expected) the statistical significance is reduced in this smaller group. Characteristics of the 65 subjects and their colds are shown in Table 1. Analysis of these and other characteristics indicated that the randomization was reasonably successful. The placebo-treated group initially had significantly more severe colds than the zinc-treated group, but several careful analyses of correlations and variance showed that initial severity (and initial number of symptoms) had virtually no effect on the duration of colds studied here. The frequency of the 10 symptoms (Table 2) was similar in both groups to those previously reported for rhinovirus colds (11).

Duration of colds. Figure 1 shows the fractions of the two groups reporting symptoms at various times after starting treatment. The two groups clearly responded very differently, and the effect of zinc is apparent from the beginning. In the zinc-treated group, sizable numbers of subjects became asymptomatic within hours (11% within 12 h and 22% within 24 h), whereas none of the placebo-treated subjects were asymptomatic within 24 h ($P = 0.10$ at 12 h; $P = 0.008$ at 24 h; by exact binomial tests). The plot for the zinc-treated group is roughly an exponential decay with a half-life of 2.7 days. That is, half of the remaining symptomatic subjects

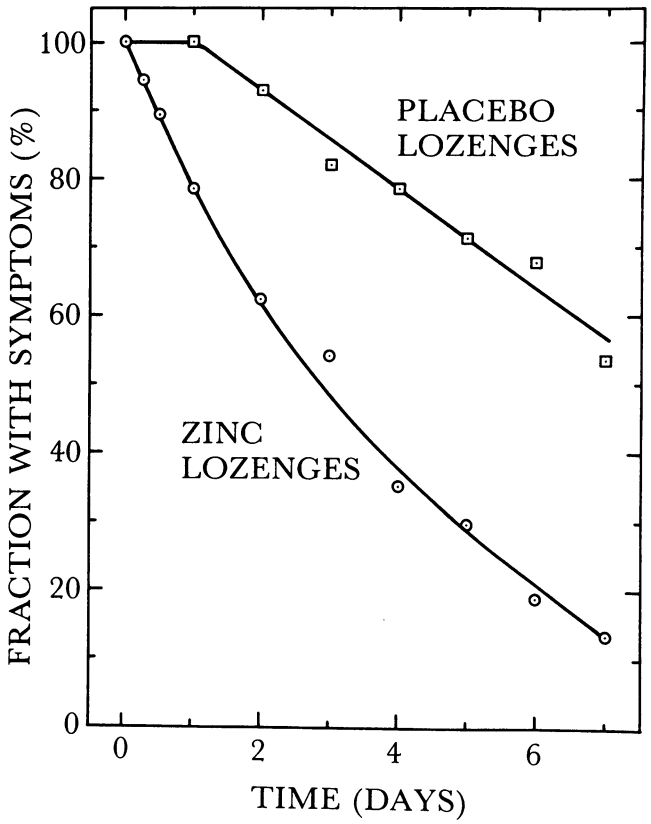

FIG. 1. Fractions of zinc and placebo groups reporting symptoms at various times after starting treatment, showing that zinc lozenges reduce duration of common colds.

became symptom-free about every 2.7 days. In contrast, the half-life in the placebo group was 7.5 days, in agreement with published findings for untreated rhinovirus colds (11). At the end of the 7-day experiment, 86% of the zinc-treated subjects reported no symptoms, compared with only 46% of the placebo-treated subjects ($P = 0.0005$).

Adequate estimates of the average duration of colds after treatment can be based on the average duration of an exponential decay curve (half-life/ln 2). This calculation yields an average duration of 3.9 days for the zinc-treated group and 10.8 days for the placebo-treated group for a 7-day reduction in average duration in this experiment.

Severity of colds. Figure 2 shows the average total severity scores. In both groups, severity scores dropped more rapidly than did the corresponding incidence figures shown in Fig. 1. Because of the initial difference in severity between the groups (discussed above), it is difficult to assess at what time these plots become convincingly divergent. However, it is clear that the half-lives of these roughly exponential decay curves are significantly different: 1.9 ± 0.3 versus 4.5 ± 1 days.

Table 2 shows how treatment reduced the frequency and severity of each of the individual symptoms after 7 days in both groups.

Dropouts. Besides the 65 subjects in the study group, 11 zinc-treated subjects and 5 placebo-treated subjects prematurely stopped recording symptoms and had to be treated as dropouts. Of those receiving zinc, seven dropped out on day 1, most of them due to objection to treatment. Of those receiving placebo, two dropped out on day 1 and the others

TABLE 2. Frequency and severity of symptoms remaining after 7 days of treatment (remaining/original)

Symptom	Frequency (%)		Severity points (%)	
	Zinc	Placebo	Zinc	Placebo
Headache	1/21 (5)	4/17 (24)	1/32 (3)	8/26 (31)
Fever	0/13 (0)	3/9 (33)	0/17 (0)	5/13 (38)
Muscle pain	1/19 (5)	4/12 (33)	1/32 (3)	7/18 (39)
Sneezing	2/18 (11)	5/19 (26)	2/26 (8)	11/27 (41)
Nasal drainage	5/27 (19)	13/24 (54)	6/45 (13)	24/49 (49)
Nasal obstruction	4/22 (18)	9/24 (38)	5/40 (13)	18/44 (41)
Sore throat	0/25 (0)	5/16 (31)	0/44 (0)	9/27 (33)
Scratchy throat	1/22 (5)	6/21 (29)	1/38 (3)	9/34 (26)
Cough	4/16 (25)	9/17 (53)	7/28 (25)	16/31 (52)
Hoarseness	1/14 (7)	5/18 (28)	1/27 (4)	11/24 (46)

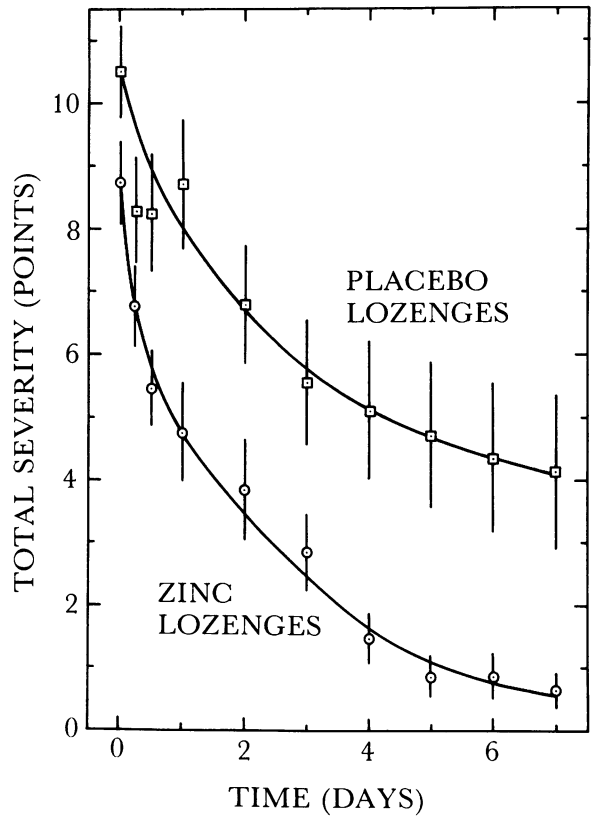

FIG. 2. Average total severity scores. Those for all common cold symptoms combined (± standard error) are lower with use of zinc lozenges.

dropped out later in the study and blamed lack of benefit. The slightly higher dropout rate in the zinc subjects (23%) compared with the placebo subjects (15%) was probably due to side effects of zinc, but this difference is far from statistically significant ($P = 0.4$).

Among the 65 subjects, 4 in the zinc group and 8 in the placebo group reported that they stopped taking lozenges prematurely, but continued reporting symptoms, and they are included in this report to maximize subjects and to treat both groups equally. The four who stopped taking zinc did poorly and biased the results presented here toward underestimating the potential of zinc.

Side effects. Side effects and complaints are shown in Table 3 for both the study group and the dropout group. Most symptoms were reported to be mild and an acceptable part of treatment. About one-half of the zinc-treated subjects reported no side effects or complaints. Unexpectedly, unpalatable taste, distortion of taste, and mouth irritation were common objections. Also, a small, transient mouth sore occurred in one subject who slept overnight with a tablet in the mouth. Emetic properties of zinc appeared in two subjects after they ingested the loading dose. Nausea was also reported after the first few tablets. Vomiting and nausea were reported to be preventable by prior ingestion of food or drink.

TABLE 3. Side effects and complaints

Parameter	Study group		Dropout group	
	Zinc	Placebo	Zinc	Placebo
No. of subjects	37	28	11	5
No. of subjects reporting side effects or complaints	20	5	7	1
No. reporting specific side effects or complaints				
Unpalatable taste	5	2	3	0
Mouth irritation	5	0	3	0
Distortion of taste	5	0	0	0
Mouth sores	1	0	0	0
Nausea or stomach distress	5	3	1	0
Vomiting	2	0	0	0
Diarrhea	2	0	0	1

DISCUSSION

These results support the hypothesis that zinc-containing lozenges can effectively treat common colds, but the exploratory nature of this research requires that it be confirmed and investigated further, building upon our findings and experience. Among the limitations of this study which need assessment are the lack of virology and the possibility of bias due to the unexpected difference in reactions to the taste and side effects of the zinc and placebo lozenges (see below).

Zinc ions are known to inhibit replication of common cold viruses (see above) at concentrations of 0.1 mM (9, 14), which is only 10-fold higher than the normal concentration in serum (15). Zinc is also reported to control recurrent herpes simplex virus skin infections (3, 8, 22). Assuming that our results are reproducible, we hypothesize that elevated local (topical) zinc ion concentrations most likely function by inhibition of viral polypeptide cleavage, but we have no direct evidence on this point and there are other possibilities. These include minimization of histamine release from mast cells and basophils at an antiviral (0.1 mM) concentration (G. Marone and L. Lichtenstein, Fed. Proc. **37**:590, 1978), immunoregulation of T-cell lymphocytes (6, 7), and prevention of excessive immunosuppressive T-cell production by means of inhibition of histamine release (19). Synergistic effects may also occur. Zinc treatment may mimic or augment a previously unrecognized antiviral function of mast cells and basophils. They are attracted in great numbers to the site of epithelial cells undergoing viral lysis. In vitro, they are reported to release large amounts of zinc ions with vasoactive amines (G. Marone, S. R. Findlay, and L. M. Lichtenstein, J. Allergy Clin. Immunol. **65**:171, 1979).

Since most viral replication in common colds occurs before or within 1 day of onset of clinical symptoms (11), any inhibition of viral replication by zinc treatment should be more effective for colds of more recent origin than those studied here (median duration, 1.0 day). We have observed that incipient colds of only a few hours in duration often seemed to abort within several hours (even in an immunosuppressed child), but this observation could not be tested in this experiment.

It may be possible to find zinc compounds and formulations which are more palatable and more effective than the unflavored zinc gluconate tablets we used. In limited trials zinc ascorbate and zinc aspartate seemed similar to zinc gluconate in their effects. However, in a companion study we found that zinc orotate was substantially less effective, perhaps because it is only very slightly soluble. Zinc sulfate and zinc chloride were not tested due to reports of very painful and caustic effects on mucous membranes.

Other protocols were briefly explored. Oral administration did not seem to work, probably because the amounts needed to produce antiviral concentrations are much greater than can be justified as safe (16). Nasal sprays seemed to work,

but required very frequent administration (every 10 to 15 min), perhaps because intranasally administered substances are rapidly cleared from the nose (1). Also, zinc nasal sprays cause nasal discomfort in concentrations in excess of 10 mM zinc. The antiviral effect of zinc may be reversible (13), so we felt it was important to administer lozenges frequently, including for a few hours past the cessation of symptoms.

Pharmaceutically acceptable forms of zinc are generally regarded as noncumulative and nontoxic when briefly ingested in the amounts used in this experiment (100 to 200 mg/day) (15–18, 20, 21). Similar amounts (with trace amounts of copper) have been administered to sickle cell anemia patients for years without apparent harm (18). These amounts have also been used for T-cell immunoregulation (6, 7) and for wound healing (17). Plasma levels may be briefly doubled by doses such as ours (15), but even chronic plasma levels three- to five-fold higher than the normal level seem without obvious harm in heritable hyperzincemia (20). Even in a case of extreme abuse of zinc gluconate (10- to 20-fold our dosage each 2 h for 4 months), the main clinical findings consisted of anemia, neutropenia, very high alkaline phosphatase, a serum zinc (antiviral) concentration 10-fold higher than normal, and a serum copper concentration 1/10th of normal. These abnormal findings were reversed with no apparent harm after withdrawal of zinc and administration of trace amounts of copper (16). Most excess zinc is not absorbed and is excreted in the feces (15).

We emphasize, however, that we used only short-term treatment (7 days or less). Habitual or long-term ingestion of large doses of zinc may be hazardous by causing imbalances with copper (16), and possibly other nutrients, and cannot be justified for treating colds or for attempting to prevent colds.

Limitations of the study and suggested improvements. We were unable to obtain desirable virological or serological services to complement the reports of the subjects. Besides these laboratory tests, future studies might also usefully include periodic ratings of signs and symptoms by a researcher.

Although the initial taste of our active and placebo lozenges is virtually indistinguishable, the zinc gluconate lozenges we used caused unexpected unpalatability and distortion of taste in many subjects which did not occur in the placebo group. These side effects are apparently amplified by prolonged and repeated contact as used in this experiment. Alterations of taste caused by the cold itself may also be involved. These effects might be lessened by suitable flavoring or other changes in the formulation.

However, it may prove difficult to find an ideal placebo for zinc gluconate lozenges, as is generally true with substances which have side effects. Perhaps potassium chloride or another addition to the placebo might help match the somewhat bitter aftertaste which some people report for zinc gluconate.

In addition to selecting the most palatable zinc lozenge and the best possible placebo, researchers can take other measures to maintain an adequate double blind. For example, in our study the subjects had no contact with each other, no knowledge of the zinc compound used, and (along with the researchers) no foreknowledge or expectation of the oral side effects which developed. Hence, they had no basis for distinguishing between zinc and placebo, and in fact there was no significant difference in response between those who reported oral side effects and those who did not. These seem to be optimum conditions for research with zinc lozenges. In future studies, both groups might be told to expect possible oral side effects due to the nature of the lozenges.

It may be argued that our results from 65 subjects are biased by lack of data from those who dropped out (16 subjects) or from those who failed to return reports at the end of the experiment (estimated 12 subjects with colds of 3 days or less, equally divided among zinc and placebo groups). Bias would occur if zinc subjects who received little or no benefit selectively dropped out or failed to return reports. We can estimate the maximum effect of such bias by assuming that all dropouts and all nonreporters in both treatment groups received no benefit and responded as if they were on placebo. In this extreme case, 40 of 54 (74%) in the zinc group would have been asymptomatic after 7 days, compared with 18 of 38 (47%) in the placebo group. Therefore, the indicated effect of zinc remains substantial and statistically strong ($P = 0.007$), and this potential bias is not large.

Nevertheless, it is desirable in future studies to reduce dropouts and nonreporting subjects. Several measures might favor this goal. Our dropouts would have been fewer if we had allowed concurrent use of other cold treatments. Improved palatability and reduced side effects would also be helpful. In this regard, it might be desirable to allow reductions in dose or modest extension of the 2-h treatment interval in those individuals who experience discouraging side effects.

ACKNOWLEDGMENTS

We acknowledge Mitchell E. Gidseg for assistance with data processing and statistical analyses, Bruce D. Korant for helpful discussions, and William L. Hightower for assistance with the experimental design. We thank Karen Lynn Eby for inspiration and Truett Laboratories for supplying the tablets used.

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