

INEFFECTIVENESS OF ZINC GLUCONATE NASAL SPRAY AND ZINC OROTATE LOZENGES IN COMMON-COLD TREATMENT: A DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL

George A. Eby, MS; William W. Halcomb, DO

Background • Zinc gluconate and zinc acetate lozenges have been reported to shorten the duration of common colds in a dose-response manner when the amount of the active ingredient, positively charged zinc ions, is sufficient.

Objective • To improve results using a zinc gluconate nasal spray with zinc orotate lozenges.

Design • Double-blind, placebo-controlled clinical trial.

Setting • Private physician's clinic in Austin, Texas.

Participants • Seventy-seven volunteers, all of whom had 2 or more signs and symptoms of common colds (with at least 1 nasal symptom) on enrollment in the study.

Methods • Zinc gluconate nasal spray (10 mmol) or placebo was used every 15 to 30 minutes, and lozenges were used each several hours to reduce duration and severity of common colds. An intention of treatment was to keep the nasal tissues wet with zinc gluconate solution during wakeful hours.

Results • After 7 days of treatment, 10 of 16 (63%) zinc-treated patients were asymptomatic compared to 9 of 17 (53%) placebo-treated patients ($P = .57$). This treatment caused olfactory region pain in some patients and did not reduce the duration or severity of common colds. Treatment did not produce anosmia, which has been reported in other studies following olfactory region administration of ionic zinc in many species and in humans from zinc nasal sprays and gels.

Conclusion • We contend that it is unethical to introduce any potentially permanent anosmia-inducing agent such as zinc or other heavy metals into the interior of the nose in a manner that could result in contact with the olfactory region to treat a temporary discomfort such as a common cold or allergy. We found no reason to recommend intranasal zinc gluconate or zinc orotate lozenges in treating common colds. (*Altern Ther Health Med.* 2006;12(1):34-38.)

George A. Eby, MS, is owner of George Eby Research, in Austin, Tex. William W. Halcomb, DO, is owner of the William W. Halcomb Clinic in Mesa, Ariz. This work was privately supported and was conducted at the William W. Halcomb Clinic in Austin, Tex. No outside financial support was provided. There are no conflicts of interest, although there is 1 year remaining on patent rights of George A. Eby, and Eby Pharma, LLC, sells zinc acetate lozenges.

Zinc gluconate lozenges (23 mg zinc each 2 wakeful hours) were first reported by Eby, Davis, and Halcomb to shorten common colds by 7 days.¹ Side effects of zinc gluconate lozenges included unpalatable taste, strong astringent feeling in the mouth (ie, "mouth-feel"), mouth irritation, and taste distortion. Complaints were attributed to the zinc compound and use of the lozenge method. Other zinc lozenges have since been studied, with lozenge efficacy being found to be directly related to total daily positively charged zinc administered and unrelated to total dosage of zinc.² However, nasal sprays seemed to the authors be

a more logical means of zinc ion administration than lozenges in the treatment of common colds, as rhinovirus infections are in the nose, not the mouth. Consequently, we wanted to test zinc gluconate nasal spray as a treatment for common colds. Another potential solution to the taste problem suggested by The Makers of Kal Inc, Canoga Park, Calif, (the lozenge manufacturer) was to use zinc orotate lozenges, which had a slightly sweet, bland taste and did not cause an astringent mouth-feel.

Before this trial, one author experienced excruciating, long-lasting intranasal (olfactory region) pain unresponsive to nasal irrigation and lasting more than 1 hour after administration of 150 mmol zinc gluconate solutions sprayed into the nose. In contrast, he found that 10 mmol zinc gluconate did not cause pain.

Consequently, we attempted to overcome the lozenge side effects by using 10 mmol zinc gluconate nasal spray every 15 to 30 minutes while awake, supplemented with zinc orotate lozenges in a double-blind, placebo-controlled clinical trial. As rhinoviral replication occurs early in common colds,³ aggressive early treatment was hypothesized to produce better results than were previously achieved with zinc gluconate lozenges, and with reduced side effects.

MATERIALS AND METHODS

The study was conducted in a private physician's clinic in Austin, Tex. Only patients diagnosed by the physician—William W. Halcomb, DO—an allergist and general practitioner—as having 2 or more signs and symptoms of common colds (with at least 1 nasal symptom) were accepted into the study. A differential diagnosis was performed to exclude those with allergic reactions or bacterial infections.

Informed consent was obtained in writing after explanation of the study and possible side effects. Potential side effects included possible oral and nasal irritation and nasal pain. The Austin-area institutional review board reviewed and approved the study.

Zinc gluconate was added to 45 cc isotonic aqueous solution in spray bottles (Ocean Nasal Spray, Fenton, Mo) to produce a 10-mmol concentration of zinc gluconate. The solution also contained benzyl alcohol as a preservative. The placebo was free of zinc but otherwise identical. We also used slightly sweet and bland (non-astringent) zinc orotate throat lozenges containing either 37 mg zinc, or, as placebo, 50 mg calcium (from calcium lactate). A 7-day supply of nasal spray and lozenges was given to each patient using a random, double-blind method wherein it was impossible for patients to receive zinc lozenges with placebo nasal spray and vice versa.

The nasal spray was to be used aggressively, in both nostrils 2 or 3 times every 15 to 30 minutes while awake with the intent of keeping the nasal tissues wet. Treatment was to be continued until symptoms had been absent for 6 hours, at which time all treatment was to be stopped. Patients were also asked to treat at bedtime and during the night if awake. One lozenge was dissolved in the mouth every 2 to 3 wakeful hours.

Each day, patients recorded at the same time of day as the initial exam the presence and severity of each of 10 common cold symptoms—headache, fever, muscle pain, sneezing, nasal drainage, nasal obstruction, sore throat, scratchy throat, cough, and hoarseness—in a diary. Symptoms were scored as being severe (3 points), moderate (2 points), minor (1 point), or absent (0 points). The patients returned their diaries to the physician on day 7 at their exit exams.

Chi-square or exact binomial statistical tests were used throughout. *P* values of less than .05 were considered statistically significant.

RESULTS

There were 77 volunteers (39 zinc, 38 placebo), of whom 28 zinc-treated patients and 27 placebo-treated patients returned report forms. Twenty-four of the 28 zinc-treated patients and 23 of the 27 placebo-treated patients had colds for 3 days or less before starting treatment, with a mean duration of 1.5 days and a median duration of 1 day for each group. Of those patients, 8 zinc-treated and 6 placebo-treated patients dropped out of the study. Consequently, the study groups consisted of 16 zinc-treated and 17 placebo-treated patients—those who had colds for 3 days or less and had not dropped out. The characteristics of the study group members and their colds are shown in Table 1. No

TABLE 1 Study Group Characteristics

Characteristics	Zinc	Placebo
Total patients	16	17
Male/female	10/6	12/5
Age range (years)	14-66	9-65
Mean age (years)	38.8	37.4
Smokers	2	1
History of any allergy	9	6
History of >4 colds per year	0	1
History of use of zinc dietary supplements	7	3
History of use of vitamin C dietary supplements	10	9
Pretreatment duration of colds		
Mean (days)	1.51	1.53
Median (days)	1.0	1.2
Range (days)	0.2-3.0	0.1-3.0
Initial total severity score		
Mean (points)	11.6	10.3
Median (points)	10.0	10.0
Range (points)	4-22	3-17
Initial Symptoms		
Mean (no.)	6.31	6.35
Median (no.)	5.5	5.0
Range (no.)	3-9	3-10

unusual characteristics or significant deviations between groups were evident.

The double-blinding was preserved throughout the study, as there was no bitterness or astringent mouth-feel from the zinc orotate lozenges and there were no other noticeable differences between the lozenges or sprays. Compliance with the protocol was reported as being good in patients who completed the study.

The hypothesis was not demonstrated. The duration of colds in patients who were treated with zinc was comparable to that of colds in patients treated with placebo (Figure 1). Two zinc-treated patients reported being asymptomatic in 24 hours. Although none of the placebo-treated patients were asymptomatic in the same period, there was no statistical significance in the difference between the groups ($P = .23$, exact binomial) for that day. After the first day, there was no difference in the rate of recovery between the 2 groups throughout the remainder of the study, and the lines representing rate of recovery had essentially the same slope and were parallel. Consequently, there was no evidence of reduction in cold duration after zinc treatment. There was no statistical difference between the 2 groups at any time during the study. By the end of the 7-day study, the statistical significance of the difference ($P = .57$, by chi square) was even less than at day 1 ($P = .23$, exact binomial).

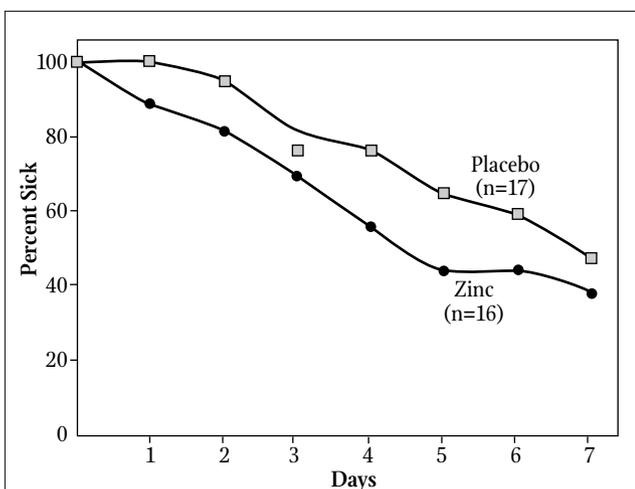


FIGURE 1 Efficacy of Zinc Gluconate Nasal Spray and Zinc Orotate Lozenges vs Placebo in Treatment of Common Colds ($P = .23$ on day 1; $P = .57$ on day 7)

The side effects of this treatment were similar to those found with 23-mg zinc gluconate lozenges¹ but not as severe (Table 2). Two zinc-treated patients and 1 placebo-treated patient reported mouth sores. Some patients objected to zinc gluconate nasal spray, reporting that it caused increased nasal discomfort (obstruction and/or soreness), and 3 reported intra-nasal pain.

Results from both zinc- and placebo-treated groups were consistent with generally accepted placebo results of many common-cold clinical trials;³ that is, one half of all patients were well in 7 days.

DISCUSSION

Even though intranasal concentration of zinc in our nasal

TABLE 2 Side Effects and Complaints

Parameter	Study group		Dropout group	
	Zinc	Placebo	Zinc	Placebo
No. of patients	17	16	8	6
No. of patients reporting side effects or complaints	7	5	4	3
Number reporting specific side effects or complaints as				
unpalatable taste	4	2	2	1
mouth irritation	3	2	2	1
distortion of taste	2	1	0	0
mouth sores	2	1	0	0
nausea or stomach distress	3	0	4	0
vomiting	0	0	0	0
diarrhea	1	1	0	0
nasal pain	3	0	1	0
nasal discomfort	5	3	2	1

spray was 100 times greater than the 0.1 mmol concentration needed to produce antirhinoviral effects according to Korant⁴ and nasal tissues were continuously kept wet with zinc gluconate solutions, we found no beneficial effect. Zinc orotate is only slightly soluble in water and is non-ionizable under physiologic conditions,⁵ which explains why these lozenges had no effect if positively charged zinc ions are the actual active ingredient, as shown in vitro by Korant⁴ and verified in vivo by Eby.² Lack of lozenge astringency should have forewarned us of their lack of utility.

Ionic zinc stabilizes cell plasma membranes⁶ and provides many other immunologic benefits.⁷ Additionally, ionic zinc used in a dose-response manner terminates mast cell histamine release and goblet cell mucous release,⁸ and we have found high-dose ionic zinc from zinc lozenges to prevent nasal mucous release effectively in both common colds and allergy.

We were concerned about toxicity from high-dose zinc (300 mg) used daily for a week but found that elimination of angina pectoris appeared to be the main unexpected side effect.⁹

With regard to intra-nasal application, our results conflicted with the highly positive results of Hirt et al,¹⁰ but supported the null results of Turner,¹¹ the limited results of Mossad for zinc gluconate nasal gels,¹² and the null results of Belongia for zinc sulfate nasal sprays.¹³ Other reports from 1901 to 2001 showed that intranasal zinc borate,¹⁴ zinc sulphocarbolate and zinc oxide,¹⁵ zinc sulfate and zinc stearate,¹⁶ and zinc sulfate (US patent 5,622,724) have been used to treat common colds, but they did not show a reduction in common-cold duration, although some were found to have mild nasal decongestant activity. Thus, in 100 years of zinc and common-cold research, there is only 1 report of a major reduction in cold duration from nasal administration of zinc. We suggest that had efficacy been truly possible, it would have been observed very early in the 20th century.

We searched for other confounders and found none. For example, the Texas Department of Health's Virological Services Division in Austin, Tex, reported that there were no reports of influenza infections in the state of Texas during or near the study period, ruling out influenza as the cause of these symptoms. Petrus demonstrated that people with a history of allergy improved more quickly using zinc acetate lozenges than did patients without a history of allergy,¹⁷ suggesting that allergy was not a cause of treatment failure. Patient characteristics also show that the history of allergy was similar in both groups (Table 1). Additionally, patients who were diagnosed as having an active allergy were excluded from the study. Perhaps colds had lasted too long before treatment initiation for zinc to be effective, but their duration was not different from that of colds in successful zinc lozenge studies. Al-Nakib at the Great Britain Medical Research Council's (MRC's) Common Cold Unit showed a statistically significant and meaningful response with zinc gluconate lozenges in the treatment of colds in only 12 patients (6 zinc, 6 placebo),¹⁸ suggesting our greater number of participants was not a cause of failure. Compliance with protocol was good because the zinc orotate lozenges were bland in taste like the placebos, and there was good blinding.

Administration of 10-mmol zinc gluconate nasal sprays was sufficiently frequent to cause both nasal irritation and occasional severe, long-lasting intra-nasal (olfactory region) pain in some patients, suggesting that 10 mmol zinc gluconate was the maximum tolerable concentration.

Zinc lozenge efficacy in reducing cold duration is directly related to the total daily positively charged zinc administered.² Efficacy occurs using pleasant-tasting, flavor-stable, astringent, and drying zinc acetate lozenges or with zinc gluconate lozenges in a fructose-only tablet base, as demonstrated by the MRC Common Cold Unit.¹⁸ These are made without flavor modifiers such as amino acids, fats, chelators, or chemical modification.

As seen in this study and others, intranasal zinc administration, though it remains a logical means of treating colds, is ineffective. This apparent inconsistency can be explained and reconciled only through biophysics and a careful consideration of biologically closed electric circuits (BCECs), as described by Nordenström.¹⁹ Existence of the mouth-nose BCEC was confirmed by one of the authors (Eby) by checking for a voltage between the mouth and the interior of the nose. Voltage between 60 and 120 millivolts (mVs; differing among individuals but not intra-individual) moves electrons and positively charged substances, such as zinc, from the mouth into the nose. This voltage rises and falls 1 to 2 mVs with the respiratory rhythm.

The electrical resistance between the mouth and the nose varies considerably and with medical importance. Individuals with frequent colds, allergies, and rhinitis have a low resistance value, between 1 and 10 Kohms. Those with an average number of colds and few or no allergies have resistances between 40 and 60 Kohms. People—particularly physicians—who are immune to common colds and have no allergies have values between 100 and 500 Kohms.

In the case of positively charged zinc that is introduced into the nasal passages by sprays, drops, and gels, zinc is repelled by the like charge of the nasal tissues, going down the throat with mucus, and is not absorbed except perhaps into the olfactory region of the nose on direct contact. Consequently, intra-oral zinc is effectively moved by the BCEC into infected tissues of the nose, and intra-nasally applied zinc is repelled.

Since this study was conducted, we have become concerned about olfactory region damage by exogenous metals. Several metals (eg, aluminum, cadmium, cobalt, mercury, manganese, nickel, zinc) have been shown to pass via olfactory receptor neurons from the nasal lumen through the cribriform plate to the olfactory bulb, and some of these metals (manganese, nickel, zinc) can cross synapses in the olfactory bulb and migrate via secondary olfactory neurons to distant nuclei of the brain. The olfactory bulb accumulates more metals than does other regions of the brain and may become damaged by them. For example, nasal irrigation with ionic zinc has been shown to physically destroy the olfactory epithelium and cause atrophy of the olfactory bulb, producing anosmia.²⁰

The persistent anosmia induced by administration of intra-nasal ionic zinc directly to the olfactory region in humans^{21,22} and

animals²³⁻²⁷ from zinc sulfate and zinc chloride and persistent anosmia in humans by zinc gluconate nasal gel^{28,29} were not observed in this trial, perhaps because the study group receiving zinc was too small. Zinc gluconate,³⁰ zinc sulfate,³¹ and zinc chloride are highly ionizable, and each releases zinc intra-nasally as Zn₂₊ (positively charged ionic zinc in aqueous solution carrying a plus-2 electrical charge capable of reacting with ligands carrying a negative charge) ions at physiologic pH 7.4. Zinc chloride remains entirely ionic at physiologic pH, whereas zinc gluconate and zinc sulfate release some lightly bound positively charged zinc species at physiologic pH. Zinc gluconate also releases some neutrally charged zinc gluconate species that are likely to cross cell membranes.²

Persistent anosmia from intra-nasal zinc administration for common colds appears permanent,^{28,29} with recent cases involving zinc gluconate having lasted more than 4 years. Upon noting olfactory region pain from intranasal zinc application, permanent olfactory damage such as anosmia might be prevented by immediate nasal irrigation for at least 30 minutes to physically remove the rhinotoxic materials as suggested by Schultz and Gebhardt.²²

Based on the human and multi-species evidence that intra-nasal zinc can be rhinotoxic if it contacts the olfactory region, the lack of evidence of efficacy in this study, and the lack of other reports of highly meaningful reduction in cold duration from any intra-nasal reports of zinc treatment for common colds other than the single report of Hirt et al, we find no reason to recommend intra-nasal zinc or zinc orotate lozenges as treatment for common colds. We suggest that it is unethical to introduce any potentially permanent anosmia-inducing agent such as zinc or other heavy metal into the interior of the nose in a manner that could result in contact with the olfactory region to treat a temporary discomfort such as a common cold or allergy.

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