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Stability Constants of Zinc Complexes Affect Common Cold Treatment Results

Recently, two articles appeared in this journal which reported negative findings with compounds of zinc formulated into lozenges as treatment for common colds (2, 4). I do not dispute their findings; rather, I offer a more constructive explanation for the differences between our respective findings than the conclusion by Farr and Gwaltney implying a propensity of Texans to fabricate tall tales (5).

Apparently, most common cold researchers have not yet realized that it is the zinc ion that is solely responsible for the marked reduction in duration of signs and symptoms of the common cold when treated with zinc lozenges and that the instability of the zinc complex is extremely important for the positive outcome of common cold experiments. My colleagues and I reported significant and meaningful reductions in the duration of signs and symptoms of common colds with highly ionizable zinc gluconate lozenges (3). Recently, D. A. J. Tyrrell's group at the British Medical Research Council's Common Cold Unit demonstrated similar reductions in the duration and severity of signs and symptoms of common colds with zinc gluconate lozenges sweetened with sugar and pleasantly flavored (1). The tablets were small, each weighing 1 g and containing 23 mg of elemental zinc. No beneficial impact on viral titer was evident over time (1).

Two studies with nonionizable zinc compounds showed completely negative results against the signs and symptoms of common colds. The first study to demonstrate lack of efficacy of nonionizable zinc compounds was reported by my colleagues and myself for zinc orotate lozenges in 1984 (3), and the second was reported by M. L. McCutcheon, University of Minnesota, Duluth (personal communication), in 1987.

In oral use in lozenge form, zinc gluconate rapidly ionizes, as does zinc combined with other ligands having low stability constants. It is very well known that if such occurs in the presence of acids having high stability constants for zinc ions at the normal pH of saliva, a new vastly stronger equilibrium immediately occurs. Such equilibrium results in extremely stable, but usually soluble, zinc complexes which cannot release their zinc ions to the saliva. Therefore, there occurs in saliva such powerful binding of zinc ions that there is no metallic taste observed and, by implication, no localized zinc activity, resulting in no observable efficacy.

TABLE 1. Summary of the various groups' findings

Research group (reference)	Zinc compound used as active ingredient (stability constant)[a]	Zinc chelator used for flavor enhancement (stability constant for zinc ions)[a]
Positive results		
Eby (3)	Zinc gluconate (50)	None
Tyrrell (1)	Zinc gluconate (50)	None
Negative results		
Douglas (2; personal communication, 1987)	Zinc acetate (40)	Tartartic acid (2,140,000)
Eby (3)	Zinc orotate (2,630,000)	None
Gwaltney (4)	Zinc gluconate (50)	Citric acid (83,000,000,000)
McCutcheon (personal communication)	Zinc aspartate (25,000,000,000)	None

[a] References 6 and 7.

Careful analysis of the formulations of lozenges used in studies by others (Table 1) shows an extreme difference in binding power for zinc ions by ligands present in successful and unsuccessful lozenge formulations, as shown herein by stability constants.

No specific mechanism has been identified by which zinc gluconate lozenges exert their action against the common cold. However, results from my studies of the effect of zinc gluconate on the signs and symptoms of common colds, as well as those of others (1), clearly show ionized zinc gluconate to be an active, but perhaps reversible, antirhinoviral-like agent in vivo. Zinc ion concentration in nasal mucus in healthy subjects has been demonstrated not to increase with use of zinc gluconate lozenges and may decline (J. M. Gwaltney, Jr., personal communication, 1984). The reversibility of the antirhinoviral effect and either absence of excess zinc ions or a decline of zinc ions in nasal mucus may help explain Tyrrell's observation of absence of reduction in viral titer in nasal mucus. Alternative explanations include immunological and physiological effects, including nonspecific cell plasma membrane protection by added zinc ions, as hypothesized by Pasternak (8).

I conclude that (i) the beneficial effect of zinc ions on the signs and symptoms of common colds is adversely affected by zinc chelators in common cold lozenge formulations (or food and drink), (ii) the solubility and stability constants of the zinc compound and the stability constant of each research zinc lozenge ingredient for zinc ions in saliva pH range must be either known or established, and (iii) all zinc lozenge ingredients, their weights, and their relevant stability constants for zinc ions should be described in articles submitted for publication so that the relevance of the results can be determined by the reader.

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***Editor's Note**: The letters of Dr. Godfrey and Mr. Eby were referred to the authors of one of the papers cited. Their response follows.*

Dr. Godfrey suggests that zinc's biologic activity was inhibited by the lozenge formulation which incorporated citric acid flavoring. Because of Mr. Eby's urging in 1985, Bristol-Myers chemists measured zinc ion concentrations produced by dissolving three different zinc gluconate preparations in water and then in saliva: (i) the lozenge containing citric acid, which was used in our clinical trials; (ii) the zinc gluconate tablet used in Mr. Eby's study; and (iii) pure zinc gluconate powder. Zinc ion concentrations were the same for all three preparations both in water and in saliva, with some complexing of zinc ions (about 30%) being found for all three preparations in saliva (H. Jones, unpublished data, Bristol-Myers Products, Hillside, N.J.). The reason that zinc complexes were not formed in the presence of citric acid may relate to the low pH created by the citric acid, as described in the following letter by Dr. Martin (R. B. Martin, Letter, Antimicrob. Agents Chemother. 32:608–609, 1988). These analytical studies of free zinc ion concentrations were completed before we submitted the Bristol-Myers lozenge to a formal study of taste matching with a placebo lozenge. The high salivary concentrations of zinc ions calculated by Dr. Godfrey are much greater than those which are cytotoxic for tissue culture cells in vitro (4), which may account for the high rate of local side effects associated with zinc lozenge use. The subjects in our placebo-matching (3) and efficacy (2) studies who received zinc lozenges had a high rate of the expected side effects of ionic zinc, including metallic taste, sore mouth, and nausea, providing additional evidence of its local bioavailability. These data suggest that the salivary zinc ion concentrations in our study were similar to those in the study of Eby et al.

Mr. Eby hypothesizes that the efficacy of the zinc gluconate lozenge may be related to salivary and not serum concentrations of zinc ions. Since the issue of biological plausibility has been raised, it should be noted that the site of infection in the common cold is the nasal mucosa and nasopharynx, extending down as far as the adenoid region (6). The mucosae of the mouth and oropharynx, which are bathed by saliva, are not believed to be infected by rhinoviruses, the most common cause of the common cold. Furthermore, dissolution of a gentian-violet-stained lozenge in the mouth shows that saliva does not reach as high as the adenoid region, much less the nasal mucosa, during swallowing (B. M. Farr and J. M. Gwaltney, Jr., unpublished data). Thus, it is difficult to see how zinc in the saliva could truly affect a nasal infection. Our two studies (2), as well as those of Dr. David Tyrrell et al. (D. A. J. Tyrrell, W. Al-Nakib, P. G. Higgins, and I. G. Barrow, Abstr. 4th Int. Congr. Virol., abstr. no. R32.3, 1987), found that zinc does not have discernible antirhinoviral activity in experimentally infected volunteers.

It is important to emphasize the importance of double blinding of randomized controlled studies of zinc efficacy through the use of taste-matched placebo lozenges. Previous studies of ascorbic acid treatment of the common cold have shown how unblinding due to differences in taste can lead to erroneous results (5). We have demonstrated that lozenges containing zinc gluconate have a strong medicinal taste that causes the subject to believe he is receiving an active medication (3). We believe that a tasteless placebo, such as the calcium lactate tablet used by Eby, is inappropriate and cannot be considered a matched placebo. This kind of disparity in the taste of active and placebo lozenges results in a systematic difference in whether the lozenge is perceived by the subject as an active or a placebo lozenge. Such a systematic difference (bias) may easily explain the magnitude of the differences in symptoms between the two treatment groups in Eby's study. The study by Eby et al. provided no data to suggest that blinding was satisfactory.

In contrast to the interpretation provided in Mr. Eby's letter, the studies by Tyrrell et al. found that prophylactic administration of zinc gluconate lozenges was not associated with significant antiviral effects or overall clinical benefit compared with placebo, whereas thereapeutic use in small numbers of subjects (six per group) appeared to be associated with reductions in symptoms and mucus weights (Tyrrell et al., 4th Int. Congr. Virol., 1987). The details of these studies have not yet been published, but we will be interested to see how placebo taste matching was documented (e.g., whether a standardized questionnaire regarding taste, side effects, and belief of being on active medication was used and whether the sample size of the taste-matching study was large enough to allow sufficient statistical power to detect important differences in these variables).

We conclude that no well-designed study with properly taste-matched placebo lozenges has yet been published to suggest efficacy of zinc gluconate lozenge therapy of upper respiratory tract viral infection. Our studies and that of Douglas et al. (1) suggest that salivary zinc concentrations equivalent to or greater than those suggested to have mild antirhinoviral effect in vitro and documented increases in serum zinc concentrations do not demonstrate an effect on upper respiratory tract viral infection in vivo.

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