Letters to the Editor

Zinc for the Common Cold

Recent articles in this journal (1, 3, 5) have followed up the original observation and clinical study of zinc gluconate as a possible oral therapy for the common cold (2). Since the original publication (2), reported results have been uniformly negative. Such observations could be accepted without further comment if the cold were not such a common and important entity in terms of discomfort and economic impact, if no reason for the negative results other than simple lack of the purported activity could be suggested.

The cited studies appear to have been well done, but in each one there are factors almost certainly unknown to the authors which may explain the negative results and cause the studies to be irrelevant to the practical treatment of the common cold.

The in vitro study (5) assessed the antiviral activities of serveral zinc salts against rhinovirus types 1A and 39. Minimal activity was seen with zinc gluconate at 0.003 to 0.1 mM and with zinc lactate and zinc oxide at 0.1 mM. The authors were limited to 0.1 mM maximum concentration because of cytotoxicity of zinc salts in the WI-38 and HeLa cell assay systems used. I have shown experimentally that one unflavored 23-mg (Zn) zinc gluconate tablet (lozenge) produces 20 ml of saliva while totally dissolving in the mouth for 10 min. Salivary zinc concentration is therefore approximately 18 mM, or between 180 and 5,900 times the concentrations previously found to be minimally effective (5) and one to two orders of magnitude greater than effective in vitro antiviral concentrations reported in references 2 to 5 and 7 cited in reference 5.

Lozenges previously used (3) contained citric acid (probably in excess over zinc) which rapidly forms very tight complexes with zinc (7, 11, 12, 15). In these complexes, no positively charged zinc ion is present, and the complex in fact has no charge at pH near 4 and, progressively, one and two negative charges as pH is raised to 8.6 and beyond (7, 9, 10, 12, 15):

$$Zn[HOCH_2(CHOH)_4CO_2]_2 \rightleftarrows Zn[HOCH_2(CHOH)_4CO_2]^+ + HOCH_2(CHOH)_4CO_2^-;$$
$$Zn[HOCH_2(CHOH)_4CO_2]^+ + HOCCO_2H(CH_2CO_2H)_2 \rightarrow Zn[HOCCO_2H(CH_2CO_2)_2] + HOCH_2(CHOH)_4CO_2H + H^+;$$
$$Zn[HOCCO_2H(CH_2CO_2)_2] \text{ at pH 4 to 8.5} \rightarrow Zn[HOCCO_2(CH_2CO_2)]^- \rightarrow Zn[HOCCO_2(CH_2CO_2)_2][OH]^{2-}$$

The effervescent tablets (1) contained bicarbonate and an excess of tartaric acid (private communication), which produces a similar result (4, 6, 8, 13, 14):

$$Zn[HOCH_2(CHOH)_4CO_2]^+ + 2\,(HOCH)_2(CO_2H)_2 \rightarrow Zn[(HOCH)_2(CO_2H)CO_2]_2 + HOCH_2(CHOH)_4CO_2H + H^+;$$
$$Zn[(HOCH)_2(CO_2H)(CO_2)]_2 \text{ at pH 4 to 8.5} \rightarrow Zn[(HOCH)_2(CO_2H)(CO_2)][(HOCH)_2(CO_2)_2]^- \rightarrow Zn[(HOCH)_2(CO_2)_2]_2^{2-}$$

Zinc gluconate is less stable than the citrate and tartrate complexes by orders of magnitude, readily giving Zn^+ (gluconate) plus gluconate ion in water. In all likelihood, previous studies (1, 3) were done with formulations in which the zinc was not only completely inactivated by complexation but carried a negative charge as well, which would tend to drive it away from inflamed tissues and probably from viral surfaces.

A further clinical study (W. Al-Nakib, P. G. Higgins, I. Barrow, G. Batstone, and D. A. J. Tyrrell, personal communication) found very significant reductions in clinical symptom score by using simple zinc gluconate lozenges, but the authors were able to show no antiviral effect. The question of whether the zinc gluconate effect is antiviral, antihistaminic, or other (unknown) remains unresolved by this study because the nasal washings used to dilute and plate out for live virus count may have diluted the zinc concentration to the point of recovery of virus viability (if the zinc antiviral effect is reversible on removal of zinc).

LITERATURE CITED

1. **Douglas, R. M., H. B. Miles, B. W. Moore, P. Ryan, and C. B. Pinnock.** 1987. Failure of effervescent zinc acetate lozenges to alter the course of upper respiratory tract infections in Australian adults. Antimicrob. Agents Chemother. **31**:1263–1265.
2. **Eby, G. A., D. R. Davis, and W. W. Halcomb.** 1984. Reduction in duration of common colds by zinc gluconate lozenges in a double-blind study. Antimicrob. Agents Chemother. **25**:20–24.
3. **Farr, B. M., E. M. Conner, R. F. Betts, J. Oleske, A. Minnefor, and J. M. Gwaltney, Jr.** 1987. Two randomized controlled trials of zinc gluconate lozenge therapy of experimentally induced rhinovirus colds. Antimicrob. Agents Chemother. **31**:1183–1187.
4. **Furlani, C., and E. Cervone.** 1962. Stability constants of zinc-citrate, zinc-tartrate, cadmium-citrate, and cadmium-tartrate complexes. Ann. Chim. **52**:564–572. [Chem. Abstr. **58**:5090b (1964)]
5. **Geist, F. C., J. A. Bateman, and F. G. Hayden.** 1987. In vitro activity of zinc salts against human rhinoviruses. Antimicrob. Agents Chemother. **31**:622–624.
6. **Jordan, J., and M. P. Ben-Yair.** 1957. Enthalpy titrations involving citrate and tartrate chelates. Ark. Kemi. **11**:239–249. [Chem. Abstr. **51**:16185i (1957)]
7. **Kovalenko, K. N., and L. I. Vistyak.** 1959. Citrate complexes of zinc in aqueous solution. Zh. Neorg. Khim. **4**:801–807. [Chem. Abstr. **54**:8410g (1960)]
8. **Kovalenko, P. N.** 1955. Influence of pH and of concentration of a solution of complex-forming components on the stability of complex ions of copper, bismuth, cadmium, zinc, and lead. Soobshch. Nauchno. Issled. Rab. Chlenov Primorsk. Otd. Vses. Khim. Ova. **1**:12–14. [Chem. Abstr. **52**:1833 (1958)]
9. **Migal, P. K., and A. Y. Sychev.** 1958. Stability of the citrate complexes of some metals. Zh. Neorg. Khim. **3**:314–324. [Chem. Abstr. **52**:19355h (1958)]
10. **Okac, A., and Z. Kolarik.** 1957. Potentiometric determination of citrate-zinc complexes. Chem. Listy **51**:2247–2253. [Chem. Abstr. **53**:13538 (1958)]
11. **Pattnaik, R. B., and S. Panai.** 1961. Citrate complexes of zinc(II) and manganese(II). J. Indian Chem. Soc. **38**:709–721. [Chem. Abstr. **56**:5629b (1962)]
12. **Pavlinova, A. V., and A. E. Protsenko.** 1960. Physicochemical study of the reaction of zinc salts with citrates. Ukr. Khim. Zh. **26**:757–761. [Chem. Abstr. **55**:12137b (1960)]
13. **Shpilev, F. S.** 1939. Isolation and investigation of the zinc tartrate complexes. Acta Univ. Voronegiensis (USSR). **10(4)**(Sect. Chem.):83–94. [Chem. Abstr. 33:7689 (1941)]
14. **Suzuki, S.** 1951. Formation of complex ions in analytical chemistry. I. Copper and zinc tartrate complexes. J. Chem. Soc. Jpn. Pure Chem. Sect. **72**:524–526. [Chem. Abstr. **46**:3444d (1951)]
15. **Vitchenko, N. K., and A. S. Tikhonov.** 1956. The reactions of

zinc with citric acid in an aqueous medium leading to the formation of complex ions. Tr. Voronezh. Univ. 43(2):57–59. [Chem. Abstr. 52:13509e (1958)]

John C. Godfrey
1649 Old Welsh Road
Huntingdon Valley, Pennsylvania 19006

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.

LITERATURE CITED

1. **Al-Nakib, W., P. G. Higgins, I. Barrow, G. Batstone, and D. A. J. Tyrrell.** 1987. Prophylaxis and treatment of rhinovirus colds with zinc gluconate lozenges. J. Antimicrob. Chemother. **20**:893–901.
2. **Douglas, R. M., H. B. Miles, B. W Moore, P. Ryan, and C. B. Pinnock.** 1987. Failure of effervescent zinc acetate lozenges to alter the course of upper respiratory tract infections in Australian adults. Antimicrob. Agents Chemother. **31**:1263–1265.
3. **Eby, G. A., D. R. David, and W. W. Halcomb.** 1984. Reduction in duration of common colds by zinc gluconate lozenges in a double-blind study. Antimicrob. Agents Chemother. **25**:20–24.
4. **Farr, B. M., E. M. Conner, R. F. Betts, J. Oleske, A. Minnefor, and J. M. Gwaltney, Jr.** 1987. Two randomized controlled trials of zinc gluconate lozenge therapy of experimentally induced rhinovirus colds. Antimicrob. Agents Chemother. **31**:1183–1187.
5. **Farr, B. M., and J. M. Gwaltney, Jr.** 1987. The problems of taste in placebo matching: an evaluation of zinc gluconate for the common cold. J. Chronic Dis. **40**:875–879.
6. **Lillen, L. G., and A. E. Martell.** 1964. Stability constants of metal-ion complexes. Special publication no. 17. The Chemical