When one thinks of the serious health problems in this nation, heart disease, cancer, and AIDS immediately come to mind largely because of the mortality associated with them. It would indeed be a bold statement to include the common cold in this list of serious health problems. Nonetheless, who would not rejoice for a cure of the common cold and relief from all those annoying symptoms like coughing, runny nose, sore throat, headache, and hoarseness. Moreover, when one considers that adults suffer from an average of 2 to 4 colds a year in this country and children from 6 to 8 colds, and that this results in millions of lost days of school and millions of lost days of work, it is evident that the common cold is a significant health problem in this nation (1). A cure for the common cold would, therefore, not only be of great therapeutic value to common cold sufferers, but would also be of enormous economic value to employers and employees. For these reasons, numerous alternative therapies have been perpetuated as cures for the common cold. One rather interesting therapy that has recently received a lot of press is the zinc lozenge. This paper will describe and attempt to resolve the contradictory research evidence for the therapeutic value of zinc lozenges and will discuss possible future research projects that may finally provide closure to the zinc lozenge story.

Contradictory Findings in Eight Controlled Trials of Zinc Lozenges for the Common Cold

Eight double-blind, placebo-controlled clinical studies have presented contradictory findings of the efficacy of zinc lozenges for the common cold. Four showed a beneficial effect of zinc lozenges while four did not show a beneficial effect.

The original study was performed in 1984 by Eby and colleagues (2) who found that the half-life of common colds in the zinc gluconate lozenge group was 2.7 days compared to 7.5 days for the group receiving placebo lozenges. They studied patients who had been ill for 3 days or less prior to treatment. Because the experimental protocol was too short (7 days) for every patients' cold symptoms to disappear, the investigators could not directly measure the average duration of cold symptoms. Instead, they extrapolated the average duration values from an exponential decay curve and reported average durations of 3.2 days and 10 days for the zinc lozenge group and placebo lozenge group, respectively. The patient was considered to no longer have a cold if the patient had none of 10 symptoms (headache, nasal drainage, etc). They further stratified their data to each individual symptom and found that most symptoms like nasal drainage and cough had half-lives of 5 to 7 days in the placebo group and about 3 days in the zinc lozenge group. Also, the severity of the cold symptoms decreased more rapidly in the zinc group with the severity of cold symptoms dropping to 60% of placebo by day 1. The possibility that the zinc group had significantly fewer and less severe initial cold symptoms than the placebo group was evaluated and shown statistically to not be a confounding factor. This landmark study stimulated others to evaluate the effectiveness of zinc lozenges.

In 1987, three more studies were reported. The Al-Nakib et al (3) study supported the 1984 findings, and the Farr et al (4) and Douglas et al (5) studies demonstrated a failure of zinc lozenges to help common cold symptoms. Human rhinovirus-2 colds were induced clinically in the therapeutic study by Al-Nakib et al who found that zinc gluconate lozenges reduced the duration of the common cold by an average of 4.8 days compared to placebo. This trial also reported beneficial prophylactic effects of zinc lozenge pretreatment on occurrence of human rhinovirus-2 colds as evidenced by a reduction in the total mean clinical score of the patients' cold symptoms. The Farr et al group induced human rhinovirus-13 and -39 common colds and used zinc gluconate lozenges containing citric acid. The zinc gluconate-citric acid lozenges did not reduce the duration or the severity of the cold symptoms. The Douglas et al group used effervescent zinc acetate lozenges and found that these lozenges actually increased the average duration of natural colds by 4.4 days compared to placebo from 7.7 to 12.1 days. These contradictory findings provoked further investigation of zinc lozenges for the common cold.

In 1989, Smith et al (6) also reported the low efficacy of zinc lozenges. Zinc gluconate lozenges did not significantly reduce the duration of the acute upper respiratory illness, and the severity of the illness in the zinc group during days 5 to 7 was decreased by only 7-8% which they reported as clinically insignificant. In 1990, the Weismann et al trial (7) supported the claim for the lack of efficacy of zinc gluconate lozenges by finding no statistically significant difference between the placebo and zinc groups.

On the contrary, the two most recent studies (1992 and 1996) reported the efficacy of zinc gluconate lozenges for the common cold. Godfrey et al (8) reported that zinc lozenge treatment when initiated on the first day of treatment reduced the average duration of colds from 9.1 days to 5.3 days. However, in their trial, if the treatment was begun on the second day, the lozenges were not nearly as effective. The most recent study by Mossad et al (1) reaffirmed the therapeutic efficacy of zinc gluconate lozenges for the common cold. The cold symptoms in the zinc group were completely resolved within a median time of 4.4 days compared with 7.6 days for the placebo lozenge group. They also analyzed the effect on each of the defined cold symptoms. For example, the zinc group had 2.5 fewer days of coughing, 2.0 fewer days of nasal congestion, 3.0 fewer days of nasal drainage, and 2.0 fewer days of sore throat. With such conflicting results from 8 clinical trials, the task now becomes how to reconcile these findings.

Resolution of Contradictory Findings

Although the trials supporting the efficacy of zinc lozenges for the common cold have their faults, these faults do not seem as significant when compared to the problems with the trials that reported a lack of efficacy of zinc lozenges. The Farr et al, Douglas et al, and Smith et al studies have all been questioned because of their use of a zinc lozenge formulation in which the zinc was inactivated (9-11). For zinc to be effective, Zn^{2+} ions must be delivered to, and be available, in the oral and oropharyngeal mucous membranes. The Zinc Ion Availability (ZIA) method of analysis has been used to explain the failure of these three studies to find a significant therapeutic effect of zinc lozenges for the common cold. ZIA serves as a measure of the bioavailability of zinc, in other words, the potential for absorption of Zn^{2+} ions into oral and oropharyngeal mucous membranes at physiological pH. Eby (12) has postulated that the ZIA value should be the proper measure of zinc lozenge strength, not the total zinc in the lozenge. Eby tried to calculate ZIA values for 7 of the 8 trials described above and found a strong correlation between the reduction of common cold duration and ZIA value. In the 1984 Eby et al trial, the ZIA value for the zinc gluconate lozenges was 100 while the ZIA value for the Al-Nakib et al (1987) study was 44. The ZIA value for Al-Nakib lozenge was lower becuase the lozenges dissolved faster and made more viscous saliva that resulted in a lower concentration of salivary Zn^{2+}. Both of these studies found zinc lozenges to have benefical effects for the common cold. The Godfrey et al (1992) study also found beneficial effects. Eby (12) could not calculate the ZIA value for this study, but the Godfrey et al lozenge was a nonchelating formulation that the authors cited as releasing 93% of the Zn^{2+} into saliva. No ZIA values have been reported for the 1996 Mossad et al study. On the other hand, the ZIA values for the zinc lozenge formulations for the Farr et al, Douglas et al, Smith et al, and Weisman et al trials (which did not find a significant benefical effect of zinc lozenges for the common cold) were -11, -55, 25, and 13.4, respectively, much lower than the ZIA values in the trials demonstrating efficacy. The Farr et al lozenge formulation included 90 mg of citric acid to mask the bad flavor of the zinc gluconate lozenge. When Zn^{2+} dissociates away from gluconate, it is strongly chelated immediately by citrate, in essence, inactivating the Zn^{2+} such that no Zn^{2+} ions are present in the oral and oropharyngeal mucous membranes at physiological pH, 7.4. The Douglas et al zinc acetate lozenge included tartaric acid that binds strongly to the Zn^{2+} ions released from acetate leaving no Zn^{2+} ions available to have a therapeutic effect. The Smith et al lozenge contained mannitol and sorbitol as well as over 16 other ingredients that may have acted to partly inactivate the Zn^{2+} ions. The Weismann et al lozenge contained only 4.5 mg of Zinc compared to 23.0 mg in the Eby et al and Al Nakib et al trials, and 13.3 mg in the Mossad et al study.

There is, therefore, strong evidence that treatment with zinc gluconate lozenges, prepared in the correct nonchelating formulation with bioavailable ions and with adequate zinc dosage, within the first 24 hours of common cold symptoms, results in a statistically significant reduction in the duration of the common cold symptoms. One can then debate the clinical significance of this reduction. Labelling this reduction in the duration of the common cold as a "cure" could be misleading because this reduction will vary from person to person, vary from cold to cold, does not eliminate the cold immediately, and has not been conclusively shown to provide prophylaxis against the common cold (3). However, reducing the duration of the common cold by several days is clinically significant when one considers the reduction in the number of lost work and school days.

Future Research Projects

The molecular basis for the therapeutic effects of zinc gluconate lozenges for the common cold has been investigated extensively, but still needs further research. Novick et al (13) have proposed that the transient elevation of Zn2+ concentration around the nasal, oral, and oropharyngeal mucosal membranes as a result of the zinc gluconate lozenge treatment results in the formation of complexes between Zn2+ ions and the intracellular adhesion molecule type 1 on rhinoviral cell membranes. This would then prevent docking and subsequent entry of the rhinovirus into mucosal epithelial cells thereby preventing further viral infection. Zn2+ may stimulate production of interferon-gamma (14) which can stop viral replication, and Zn2+ inhibits the production of viral capsid peptides which also inhibits viral replication (15,16). Zn2+ has also been shown to play a critical role in cellular immunity. Zinc deficient patients have decreased CD8 Killer T Cells (which attack virally infected cells) and have decreased interleukin-2 production (which is necessary for T-lymphocyte proliferation). Therefore, the administration of zinc supplements in these deficient individuals could possibly help reduce the number of common colds in this subpopulation of common cold sufferers (17).

Reduction and maybe even ellimination of the side effects of zinc gluconate lozenges is another future project. The Mossad et al study reported bad taste and nausea (1). More importantly, as the public becomes more and more enthused about zinc, the possibility of people taking large quantities (over a gram) to prevent the common cold could be dangerous when one considers the evidence that excessive zinc intake results in hypocupremia and an impaired immune system (18,19).

In conclusion, although the molecular mechanism of the therapeutic effect of zinc lozenges for the common cold has not been pinpointed, strong evidence from clinical trials makes zinc gluconate lozenges an appealing potential treatment for the common cold.

REFERENCES

1. Mossad SB, Macknin ML, Medendorp SV, Mason P. "Zinc gluconate lozenges for treating the common cold. A randomized, double-blind, placebo-controlled study." Annals of Internal Medicine. 1996; 125: 81-88.

2. Eby GA, Davis DR, Halcomb WW. "Reduction in duration of common cold by zinc gluconate lozenges in a double-blind study." Antimicrob Agents Chemother. 1984; 25: 20-24.

3. Ał Nakib W, Higgins PG, Barrow I, Batstone G, Tyrrell DA. "Prophylaxis and treatment of rhinovirus colds with zinc gluconate lozenges." J Antimicrob Chemother. 1987; 20: 893-901.

4. Farr BM, Conner EM, Betts RF, Oleske J, Minnefor A, Gwaltney JM Jr. "Two randomized controlled trials of zinc gluconate lozenge therapy of experimentally induced rhinovirus colds." Antimicrob Agents Chemother. 1987; 31: 1183-7.

5. Douglas RM, Miles HB, Morre BW, Ryan P, Pinnock CB. "Failure of effervescent zinc acetate lozenges to alter the course of upper respiratory tract infection in Australian adults." Antimicrob Agents Chemother. 1987; 31: 1263-5.

6. Smith DS, Helzner EC, Nuttall CE Jr, Collins M, Rofman BA, Ginsberg D, et al. "Failure of zinc gluconate in treatment of acute upper respiratory tract infections." Antimicrob Agents Chemother. 1989; 33: 646-8.

7. Weismann K, Jakobsen JP, Weismann JE, Hammer UM, Nyholm SM, Hansen B, et al. "Zinc gluconate lozenges for common cold. A double-blind clinical trial." Dan Med Bull. 1990; 37: 279-81.

8. Godfrey JC, Conant Sloane B, Smith DS, Turco JH, Mercer N, Godfrey NJ. "Zinc gluconate and the common cold: a controlled clinical study." J Int Med Res. 1992; 20: 234-46.

9. Godfrey JC. "Zinc for the common cold." Antimicrob Agents Chemother. 1988; 32:605-6.

10. Eby GA. "Stability constants of zinc complexes affect common cold treatment results." Antimicrob Agents Chemother. 1988; 32: 606-7.

11. Zarembo JE, Godfrey JC, Godfrey NJ. "Zinc (II) in saliva: determination of concentrations produced by different formulations of zinc gluconate lozenges containing common excipients." J Pharm Sci. 1992: 81; 128-30.

12. Eby GA. "The zinc lozenge and common cold story." In: Berthon G, ed. Handbook of Metal-Ligand Interactions in Biological Fluids. New York: Marcel Dekker, Inc., 1995; 1182-1190. see http://www.coldcure.com/html/opinion.html

13. Novick SG, Godfrey JC, Godfrey NJ, Wider HR. "How does zinc modify the common cold? Clinical observations and implications regarding mechanism of action. Medical Hypotheses. 1996; 46: 295-302.

14. Salas M, Kirchner H. "Induction of interferon-gamma in human leukocyte cultures stimulated by Zn2+." Clin Immunol Immunopathol. 1987; 45: 139-42.

15. Korant BD, Butterworth BE. "Inhibition by zinc of rhinovirus protein cleavage: interaction of zinc with capsid polypeptides." J Virol. 1976; 18: 298-306.

16. Geist FC, Bateman JA, Hayden FG. "In vitro activity of zinc salts against human rhinovirusees." Antimicrob Agents Chemother. 1987; 31: 622-4.

17. Prasad AS, Meftah S, Abdallah J, Kaplan J, Brewer GJ, Bach JF, et al. "Serum thymulin in human zinc deficiency." J Clin Invest. 1988; 82: 1202-10.

18. Prasad AS, Brewer GJ, Schoomaker EB, Rabbani P. "Hypocupremia induced by zinc therapy." JAMA. 1978; 240: 2166-8.

19. Chandra RK. "Excessive intake of zinc impairs immune response." JAMA. 1984; 252: 1443-6.