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Zinc lozenges as cure for the common cold – A review and hypothesis

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SUMMARY

A 7-day reduction in duration of common colds was shown by Eby et al. in 1984 using 23 mg zinc gluconate throat lozenges. Over the following 25 years, 14 double-blind, placebo-controlled, randomized clinical trials produced widely differing results with about one-half showing success and the remainder showing failure. Positively charged, ionic zinc (iZn), but not bound zinc, is strongly astringent, antirhinoviral, increases interferon-gamma (IFN-γ) 10-fold, inhibits intercellular adhesion molecule-1 (ICAM-1) and inhibits the release of vasoactive ingredients from mast cell granules. Solution equilibrium chemistry analytical techniques showed lozenge iZn fraction varying from 0% to 100% of total lozenge zinc between trials, with zinc acetate (ZA) releasing 100% iZn, zinc gluconate (ZG) releasing 72% iZn and other zinc compounds releasing much less or none at physiologic pH 7.4. Since only iZn has in vitro benefits, iZn variations are hypothesized to have produced the widely varying clinical results. In support of the iZn hypothesis, lozenge iZn and total daily iZn in trials were found highly correlated with reductions in common cold durations with statistical significance for mean duration ($P < 0.001$) and median duration ($P < 0.004$), while total zinc (iZn plus bound) showed no correlation with changes in duration. Duration reductions (mean 0 days, median 0.43 days) for multi-ligand ZG and ZA lozenges differed significantly from duration reductions (mean 3.37 days, median 2.9 days) for single ligand ZA and ZG lozenges ($P < 0.001$) showing that additive ligands as flavor-masks damaged or eliminated efficacy. Five of 6 trials with lozenges whose zinc compositions had a first stability constant of 1.7 or less succeeded, while only 2 of 9 trials of lozenges with higher stability succeeded ($P < 0.02$). From the strong, multiple statistical relationships found, it is inferred that iZn is the active ingredient in zinc lozenges for colds, as it is in vitro against rhinoviruses, and that solution chemistry analytical techniques used at physiological pH are correct means for lozenge iZn analysis. Zinc lozenges slowly dissolving in the mouth over a 20–30 min period releasing adequate iZn ($\geqslant$18 mg) used each 2 h are hypothesized to shorten common colds by 6–7 days, which is a cure for the common cold. Due to inadequate lozenge iZn very few of more than 40 different brands of zinc lozenges on the US market are expected to have any effect on the duration or severity of common colds.

Introduction

Viral pathogens primarily associated with upper respiratory tract infections, common colds, include several hundred picornaviruses (notably, rhinoviruses and enteroviruses), coronaviruses, adenoviruses, parainfluenza viruses, influenza viruses, and respiratory syncytial viruses. Consequently, a vaccine-based cure for the common cold has been hindered by the large number of viruses that can cause a common cold. Non-influenza-related viral respiratory tract infections (common colds) are the most frequent reason for office visits by adults and children to general practice physicians, accounting for over one hundred million primary care visits and an economic impact of over $40 billion per year in the United States. Inappropriate prescription of antibiotics to treat viral common colds occurs in up to 60% of office visits. This results in unnecessary costs, contributes to antibiotic resistance and exposure to severe antibiotic side effects especially when fluoroquinolones are used. There is a great public need for a safe and effective cure for common colds [1], and zinc lozenges have been hypothesized to be the cure the common cold.

In vitro, positively charged, ionizable zinc (iZn), but not bound zinc, demonstrates strong antirhinoviral activity by inhibiting the normal cleavages by which the viral polypeptides are processed [2–10]. Ionic zinc inhibits intercellular adhesion molecule-1 (ICAM-1) [11]. Ionic zinc increases interferon-gamma (IFN-γ) 10-fold [12,13]. Ionic zinc inhibits the release of histamine and leukotrienes from basophils and mast cells [14], protects cell-plasma membranes (including mast and goblet cells) [15] and has benefit in treating allergy [16–18]. Ionic zinc also has antiviral effects against other respiratory viruses including herpes virus [16,19] and respiratory syncytial virus [20].

Regardless of in vitro benefits, results of the 15 placebo-controlled, double-blind, randomized clinical trials (RCTs) of zinc

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lozenges for common colds conducted from 1984 to 2009 have ranged from reducing durations of colds by 7 days in the original Eby et al. RCT [21], to lengthening colds by 4.4 days in the Douglas study [22]. There was no relationship between total zinc in the lozenges and effects on duration of colds. This unusual and unexpected range of responses caused a therapeutic controversy.

Variations in clinical results were hypothesized to have been caused by variations in lozenge iZn [17,24,25]. Solution equilibrium chemistry computations from the field of inorganic chemistry are hypothesized to provide the only scientifically valid means to determine iZn availability from lozenges. Variables for these computations include metal and ligand stability constants, pH and pK values, concentrations and temperature. Absorption of useful iZn from throat lozenges is local – in the oral, throat and nasal tissues only – consequently the only pH that has meaning in treatment of colds is hypothesized to be physiologic pH 7.4. In these computations, temperature was held constant at 37 °C and zinc concentration was held constant at 5 mmol iZn. Minor variations in these variables in the range used in these RCTs are not believed relevant. Very few common zinc compounds release substantial iZn at physiologic pH, and zinc chloride, sulfate, acetate and gluconate are the only known sources [23]. Positively charged ionic zinc species always produce a characteristic metallic taste and a drying and astringent mouth-feel.

Using solution chemistry computations as a foundation, Fig. 1 shows great variability in the amount of iZn between zinc compounds and by pH. The lines in Fig. 1 (percent iZn) are the sums of all positively charged zinc species by pH taken from detailed computations performed by solution chemists [16–18,23–28] and specifically from the article "Zinc Lozenges: Cold Cure or Candy? Solution Chemistry Determinations" [18]. At each pH, the remainder of zinc (total zinc minus iZn) is bound zinc. All computations utilized the US Department of Commerce, National Institute of Standards and Technology (NIST) solution equilibrium inorganic chemistry data base [23]. These computations do not include interaction of iZn with proteins, lipids, and carbohydrates present in saliva and oral and nasal tissues. Although these interactions are important, they mainly result in a requirement for a much larger concentration (~700-fold) of iZn than would be required for biological effects in vitro [29].

From Fig. 1, at stomach acid pH each of these compositions releases ~100% iZn and nearly zero bound zinc. In the saliva – measured at pH 5 – each zinc composition, except zinc gluconate–citrate (ZG–C), releases large amounts of iZn explaining why most commercial zinc lozenges except ZG–C taste astringent. Consequently, oral astringency is not a reliable indicator of iZn at physiologic pH 7.4. Zarembo et al. [30] reported zinc gluconate–glycine (ZGG) to release 92% iZn (the data point in Fig. 1). That measurement was taken at salivary pH 5.0 where the effect of the second ligand (glycine) is weak in reducing iZn, not at physiologic pH 7.4 where glycine action is much stronger [18,28]. At pH 7.4 only zinc acetate (ZA) releases 100% iZn.

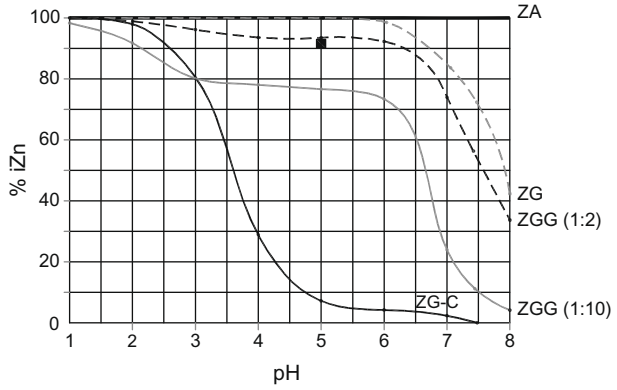

Fig. 1. Percentage of zinc present as iZn by pH. At physiologic pH 7.4, zinc acetate (ZA) yields 100% iZn, zinc gluconate (ZG) yields 72% iZn, zinc gluconate with a 1:2 M ratio of zinc gluconate to glycine [ZGG (1:2)] yields 57% iZn, zinc gluconate with a 1:10 M ratio of zinc gluconate to glycine [ZGG (1:10)] yields 11% iZn, and zinc gluconate with a 1:1.3 M ratio of zinc gluconate to citrate or zinc citrate (ZG–C) yields zero iZn.

The first stability constant (K_1) logarithm of zinc acetate is 1.03, which equals 10 (10^1) meaning that zinc is totally ionic in solution at each pH shown [32]. The K_1 for zinc gluconate is 1.7, which equals 50 ($10^{1.7}$), and zinc is only slightly less ionic than zinc acetate in solution [27,31]. The K_1 for zinc tartrate is 2.9, which equals 794 ($10^{2.9}$), and it yields only 1/8 of the amount of ionic zinc found in zinc acetate [31–33]. K_1 for both zinc glycinate and zinc citrate is 4.8, which equals 63,096 ($10^{4.8}$) yielding much less zinc than other compositions shown or no ionic zinc, respectively, at physiologic pH 7.4 [27,31,33]. The K_1 for zinc aspartate is 5.8, which equals 630,957 ($10^{5.8}$), which is 63,000 times more tightly bound than zinc acetate yielding no ionic zinc at physiologic pH [31,32] Zinc compositions with very low chemical stabilities release much more iZn (and little or no bound zinc) at physiologic pH than those with higher stabilities, which release mainly bound zinc. Unstable zinc compounds react with other ingredients in lozenges in situ and in saliva producing reaction products having vastly different chemical properties, including elimination of iZn.

There are multiple hypotheses being tested in this analysis. The hypothesis that solution equilibrium chemistry is an appropriate means of determining the amount of iZn at physiologic pH of the oral and nasal tissues and blood is suggested to be valid only if the iZn dose–response statistical relationships are found to be strong. The hypothesis that the only relevant pH is physiologic pH is supported by countless data showing that tissues such as the oral and nasal tissues and blood are normally at "physiologic" pH 7.4. This pH is important for this analysis since the amount of iZn varies greatly by pH as well as between zinc compositions.

Some researchers have advocated that the relevant pH is pH 5.0, salivary pH. Reanalysis of the amount of iZn found in each trial at pH 5.0 showed that only the 1992 Godfrey et al. ZGG trial [42] was impacted strongly by this shift. Rhinoviruses are believed to infect nasal and adenoid cells and not the saliva or oral cells; consequently physiologic pH is hypothesized to be the correct pH to make iZn observations.

Methods and procedures

In a search for evidence of a zinc lozenge cure for the common cold, this review considered all English-language reports concerning zinc lozenges for colds indexed on PubMed from January, 1984 through September 28, 2009. The search consisted of zinc and "common cold" (120 articles), zinc and "common colds" (18 articles) and an RCT published previously only in 2 books. All in vitro reports of zinc and rhinoviruses (37 articles) were also reviewed. No zinc and common cold RCT was excluded resulting in a thorough review of the literature. Fifteen RCTs were found and analyzed for their solution equilibrium chemistry data and clinical results. In some of these RCTs, critical solution equilibrium chemistry information necessary to determine the amount of active ingredient (iZn) was omitted from the original article, but was found in supportive literature. This mainly concerned unreported additions of food-acids as flavor-masks to eliminate the metallic taste and astringent mouth-feel of iZn, and identification of zinc compounds that do not release iZn.

Application of the fractional amounts of zinc as iZn shown in Fig. 1 for each zinc composition allowed the computation of the

amount of iZn in each of the trials and the statistics showing the strong relationship between iZn and effect on duration of colds.

In 1984 Eby et al. [21] first reported zinc gluconate (ZG) lozenges in a 65 patient RCT to be an effective treatment for common colds. One 23-mg zinc (16.56 mg iZn) lozenge or calcium lactate placebo was dissolved in the mouth every 2 wakeful hours after an initial double dose (9 doses per day after the first day loading dose at 12 doses). After 7 days of treatment, 86% of 37 zinc-treated subjects were asymptomatic, compared with only 46% of 28 placebo-treated subjects ($P = 0.0005$) producing statistically significant and meaningful benefits. Zinc lozenges shortened the median duration of colds by 4.8 days and their mean duration by 7 days. Patients in both groups had been ill an average of 1.6 days prior to admission. The groups were well balanced for 12 patient characteristics, and if dropouts and those that did not return reports were hypothetically considered as negative responders, the positive results remained statistically sound ($P = 0.007$). The ZG lozenges were unflavored 1-g compressed tablets which dissolved in 20–30 min in the mouth. They contained 23 mg of zinc as active ingredient or 50 mg of calcium lactate as inactive ingredient. Tablets 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). Lozenges had a chalky, non-bitter taste and were strongly drying and astringent.

In 1987 Al-Nakib et al. [34] at the British Medical Research Council Common cold Unit (CCU) in Salisbury, England used ZG lozenges containing 23 mg zinc (16.56 mg iZn) used 9 times per day to treat HRV-2 rhinovirus-induced colds in a 12 patient RCT. Lozenges dissolved in the mouth in 20 min. Zinc reduced the daily mean clinical score (the severity average of a number of symptoms) from 8.2 in the placebo-treated group to 5.7 in the zinc-treated group, and the reduction was statistically significant on the second day after virus challenge ($P = 0.05$). The total mean clinical score (the sum of the mean clinical scores for each day) was reduced from 41.0 in the placebo-treated group to 27.2 in the zinc-treated group ($P = 0.05$). Objective scores including mean nasal secretion weight ($P = 0.05$), and total tissue counts ($P = 0.05$) were also significantly reduced in the zinc group compared with placebo. The strongly anisette flavored 1-g wet granulated compressed lozenges were designed by Rinaldo Pellegrini, MD, Ph.D. of RBS Pharma-Milan in Milano, Italy. They had a fructose and methylcellulose tablet base with magnesium stearate lubricant, and they produced a strongly drying and astringent mouth-feel [16]. These non-bitter, pleasant tasting ZG lozenges were estimated to have shortened the mean duration of colds by 4.8 days compared to a matched placebo [16]. The Al-Nakib et al. [34] article was reviewed and extended in a book [16] to include the estimated reduction in duration data in full cooperation with CCU personnel who also wrote forewords. Fructose is the only carbohydrate sweetener that does not become bitter after aging for several weeks when combined with zinc gluconate.

In an accompanying prophylaxis study by Al-Nakib et al. [34], a total of 57 volunteers received lozenges of either ZG (23 mg zinc) or matched placebo every 2 h while awake during a period of four and a half days. They were challenged with tissue culture infecting doses of human rhinovirus 2 (HRV-2) on the second day of medication with zinc or placebo and were monitored daily for symptoms and signs of developing colds and laboratory evidence of infection. Treatment in the prophylactic trial showed the response to zinc-treatment to have been statistically significant on the first day after viral challenge, with zinc reducing total clinical scores compared to placebo (8.2 vs. 5.7), mean nasal secretion weight, and virus excretion. Even though treatment was stopped on the third day after viral challenge, mean clinical scores for the zinc-treated group on the fourth, fifth, and sixth days remained lower than for the placebo-treated group – by 30% on day four, 38% on day five, and 20% on the sixth day. This was the only study to produce meaningful and statistically significant positive results in the 30-year history of the CCU.

The unpublished 1987 trial of McCutcheon et al. was described in a letter [16] as using 24 mg of zinc from zinc aspartate (ZP) nine times daily. It was the first trial to have used non-ionizable zinc (0 mg iZn). The trial was comprised of 49 university students having had common cold symptoms 3 days or less before enrollment in the study. There was no metallic taste, no astringency and no reduction in the duration of colds [16,17]. Berthon and Germonneau [35] demonstrated that iZn is essentially unavailable (totally bound) in zinc aspartate at physiologic pH. These 1.5 g sucrose and fructose lozenges also contained calcium ascorbate, bee propolis, slippery elm, vitamin A palmitate, 2 sugars, 2 stearates, Duratex™, and 3 spray-dried flavor oils in both the zinc aspartate and placebo lozenges [16].

The first RCT of zinc lozenges for colds that mentioned addition of a food-acid flavor mask was the 1987 report by Farr et al. at the University of Virginia [36]. This study in 77 patients used hard-boiled 4.5 g sugar and corn syrup lozenges containing 23 mg zinc from gluconate, 90 mg citric acid (2% of lozenge weight) and lemon flavoring. The lozenges or a matched placebo were given eight times daily to treat laboratory-induced HRV-13 and -39 colds. The significance of the added citric acid was unknown until a 1988 article by solution chemist R. Bruce Martin, Ph.D., was published showing the absence of ionic zinc and presence of negatively charged zinc species at physiologic pH [27]. The lozenges were pleasant tasting, non-astringent, non-drying, and non-metallic in flavor and were essentially indistinguishable from placebo. The reaction product was tightly bound zinc citrate (0 mg iZn). The active lozenges appear to have lengthened the mean duration of colds by at least one day compared to placebo since tissue usage was 50% higher in the active group than the placebo group on day 7 of the trial. This formulation is the most common zinc lozenge formulation on the United States market and results in zinc lozenges that do not shorten common colds [37].

The Douglas et al. [22] 1987 RCT report omitted mention of additive food acids in their "effervescent" zinc acetate lozenges used to treat natural colds in 63 subjects in Adelaide, South Australia. The average duration in the zinc-treated group was 12.1 days versus an average of 7.7 days in the placebo-treated group. Cold duration was increased 4.4 days by strongly effervescent zinc acetate (ZA) 10-mg zinc lozenges used 6.4 times daily compared to placebo. A letter from the lozenge designer and manufacturer, Faulding LTD, Adelaide, South Australia, indicated that the lozenges contained zinc acetate plus tartaric acid and sodium bicarbonate (ZA–TB) sufficient to result in strong oral effervescence [16]. Zinc acetate dissociates in the presence of these added ingredients and forms several tightly bound reaction products including zinc carbonate, which is non-soluble and non-ionizable [38] and negatively charged zinc tartrate species (0 mg iZn) [39]. These zinc lozenges appear to have released sufficient negatively charged zinc species that they neutralized native iZn from mast cell granules of the infected nasal epithelium, resulting in significantly worsened cold symptoms. Gluconate binds iZn about 10 times less strongly than tartrate [27]. Minor ingredients included talc and magnesium stearate lubricants, color and flavor.

Smith et al. in 1989 reported on ZG lozenges with 23 mg zinc lozenges (16.56 mg iZn total) used nine times per day in 110 patients with natural colds [40]. These lozenges reduced symptom severity compared to placebo on days 4–7 ($P = 0.02$), but they had no effect on duration of colds. These lozenges also contained sucrose, fructose, sorbitol, mannitol, mineral and acid stearates, Methocel®, pineapple powder and three spray-dried flavors in both the zinc and placebo lozenges. This clinical trial is the only trial in

this review to be considered an outlier. Such status resulted from extreme bitterness, equivalent to their ultra-bitter placebo containing sucrose octaacetate, which prevented patients from using lozenges, with expectoration and non-use of lozenges being common (personal communication, C.B. Goswick, 1989) [16].

Weisman et al. [41] in 1990 studied ZG lozenges given 10 times per day in a RCT of 130 subjects in Copenhagen, Denmark to treat natural colds. They found no statistically significant effect of the lozenges on cold duration. Lozenges contained 4.5 mg zinc (3.24 mg iZn) in a flavored, hard-boiled maltitol-syrup candy, which was the highest concentration of zinc possible in that candy base without extreme bitterness. Maltitol is a liquid food ingredient consisting of 75% dry substance containing 72–73% hydrogenated disaccharides, a maximum of 8% D-sorbitol with approximately 20% of the hydrogenated disaccharides having a degree of polymerization higher than two.

In 1992 Godfrey et al. [42] studied zinc gluconate–glycine (ZGG) lozenges containing 23.7 mg zinc (1 mol zinc gluconate to 10 mol glycine) in 4.5 g orange-flavored, hard boiled, sucrose and corn syrup lozenges in an RCT. Lozenges were used an average of 8.1 times per day. The study involved 73 patients in the treatment of natural colds. Zinc-treated colds lasted an average of 4.86 days compared with placebo-treated colds at 6.13 days, and were shortened 1.3 days compared to placebo ($P < 0.05$). The reaction product was mostly bound zinc glycinate (2.60 mg iZn). Their assertion of a 42% reduction in the duration of colds was not supported by their placebo-controlled data.

In a 1996 RCT involving 99 subjects by Mossad et al. [43], 13.3 mg zinc ZGG lozenges (1:2 M ratio of zinc gluconate to glycine) used six times daily meaningfully reduced the median cold duration by 3.2 days [4.4 days for zinc-treatment vs. 7.6 days for placebo-treatment ($P < 0.001$)]; and reduced the mean duration by 4.1 days [5.2 days for zinc-treatment vs. 9.3 days for placebo-treatment ($P < 0.001$)]. These 4.4 g hard boiled candy lozenges also contained sucrose, corn syrup, lemon and lime flavor oils. The reaction product was one-half zinc glycinate (7.58 mg iZn).

Macknin et al. [44] in a 1998 RCT of 249 children found that ZGG lozenges having 10 mg zinc used six times daily did not affect the duration of children's colds. These 3.75 g hard boiled candy lozenges also contained sucrose, corn syrup and cherry-flavor oil. Time to symptom resolution was 9 days for both groups, and the daily resolution rate of all cold symptoms appeared identical for both groups when plotted on a graph. No difference in days absent from school was found. The reaction product was about one-half zinc glycinate (5.70 mg iZn).

Petrus et al. [45] in 1998, using zinc acetate (ZA) lozenges, found significant reductions in mean duration (3.8 days zinc, 5.1 days placebo, for a 1.3 days difference ($P = 0.008$) and reductions in severity of common colds using 9 mg of zinc (9 mg iZn) in 2.7-g lozenges in 101 patients. Lozenges were small zinc acetate lozenges consisting of a dextrose tablet base, 2.5% glycerol monostearate lubricant, stevia and peppermint oil on silica gel compressed with a force sufficient to allow them to dissolve in 15 min in the human mouth. Lozenges were used each 1.5 h on the first day and every 2 h on following days during wakeful hours (9.9 lozenges per day). These lozenges meaningfully relieved cold symptom faster in patients with a history of allergy (but without active allergy symptoms) ($n = 46$) compared with allergy-negative subjects ($n = 55$) (3.5 days vs. 7.6 days $P < 0.04$).

Prasad et al. [46] in 2000, found significant and meaningful efficacy using 12.8 mg zinc (12.8 mg iZn) in 4.0-g compressed ZA lozenges to treat natural colds in 48 patients. Lozenges were used each 2–3 h (6.25 per day). Fifty percent of zinc recipients were well in 3.8 days and 50% of placebo recipients were well in 7.7 days (3.9 days median difference). The zinc group also had shorter mean durations of colds (4.5 vs. 8.1 days $P < 0.01$, a 3.6 day mean reduction), decreased total severity scores for all symptoms ($P < 0.002$) with good placebo blinding, mild or no side effects and little difference in side effects compared with mild tasting placebo. Effect was sufficiently strong that they suggested seeing a physician for a bacterial infection if symptoms were not significantly improved after using these ZA lozenges for 3 days. These zinc acetate lozenges were peppermint-flavored consisting of an agglomerated dextrose tablet base, 2.5% glycerol monostearate lubricant, stevia and peppermint oil on silica gel compressed with a force sufficient to allow them to dissolve in 30 min in the mouth.

Turner and Cetnarowski tested ZGG and ZA lozenges in 2000 using both natural colds and induced rhinovirus colds against placebo in a RCT [47]. Lozenges were used six times daily and were given while patients were symptomatic. The 13.3-mg zinc ZGG lozenges (7.58 mg iZn) lengthened the median duration of natural colds ($n = 139$) by half a day and shortened the median duration of human rhinovirus (HRV)-39-induced colds ($n = 136$) by one day compared to placebo. They were described as identical to the ZGG lozenges tested previously by Mossad et al. [43]. The 5-mg ZA lozenges lengthened the median duration of natural colds ($n = 143$) by half a day and had no effect on induced colds ($n = 133$) compared to placebo. The ZA lozenges with 11.5 mg zinc had no effect on median duration of natural colds ($n = 139$) and shortened HRV-39-induced colds ($n = 137$) by 0.25 day compared to placebo. These hard boiled ZA lozenges contained sucrose, glucose syrup, artificial flavoring (citrus), artificial colors, hydrogenated palm kernel oil, cotton seed oil, soy lecithin and the highly acidic Panoden™ surfactant. At the high cooking temperatures (157 °C) used, the added ingredients reacted with ionic ZA to produce reaction products of zinc stearate, zinc oleate, and zinc palmitate waxes (ZA–SOP), which are non-soluble, totally bound (0 mg iZn) and incapable of releasing iZn [48]. These zinc compounds were found to be fat soluble, non-miscible, non-ionic, non-astringent and hydrophobic. The lozenges were patented under US Patent Number 6,242,019 to produce a "substantial reduction in the unpleasant organoleptic sensations associated with the release of functional ingredients from the confection in the oral cavity".

Eby and Halcomb reported in 2006 zinc orotate (ZO) lozenges (37 mg zinc) used 9 times daily along with a 10 mM zinc gluconate saline nasal spray used each 15–30 min to have no effect on cold duration in a 75 person RCT [49]. Zinc orotate is tightly bound (0 mg iZn) and essentially insoluble [50], and non-soluble compounds do not release iZn. These 3.6 g lozenges also contained gum guar, cellulose, silica, and vegetable stearine [16]. Lozenges were nearly insoluble and required more than 1 h to dissolve in the mouth. This study was the second component of our 1984 clinical trial [21], and its results were published in 2 mid-90s books [16,17], but were not published as a peer reviewed article until 2006.

The 2008 Prasad et al. [11] RCT of 50 patients used ZA hard boiled candy lozenges containing 13.3 mg zinc (13.3 mg iZn). Lozenges were given 6.9 times per day, with a mean reduction of cold duration of 3.1 days in all patients (4.0 vs. 7.1 days $P < 0.0001$), and 3.85 days in a subgroup of blinded patients (3.54 vs. 7.39 days; $P < 0.0001$). Severity of symptoms over the 10 days of the study was meaningfully and significantly reduced in the zinc-treated group ($P < 0.0002$). These 3.8-g hard boiled lozenges also contained sucrose, corn syrup and cherry oil, and were prepared using the open pot batch method with the active ingredient (anhydrous zinc acetate) added last. Blinding was adequate and adverse effects between the groups did not differ significantly. Activation of monocytes and macrophages was decreased by iZn, most likely due to antioxidant effect of iZn. Intercellular adhesion molecule-1 (ICAM-1) was significantly decreased with iZn compared to placebo ($P < 0.04$), probably due to decreased nuclear factor-kappaB (NF-κB) activation. They suggested that the decrease in plasma

ICAM-1 levels due to iZn therapy decreased docking of the cold viruses on the surface of somatic cells. Human rhinoviruses must "dock" with ICAM-1 on the surface of somatic cells to produce infection [51]. Thus, iZn acts as an antirhinoviral agent by reducing ICAM-1 as well as being directly antiviral to rhinoviruses [2–10] and by increasing interferon-gamma [12,13].

Results from these 15 RCTs are organized into Tables 1–3 and are presented in Fig. 2a and b to test the hypothesis that iZn from lozenges might be the cure for the common cold, while total daily zinc (iZn plus bound zinc) intake is hypothesized to have no relationship with efficacy.

Results

To determine if zinc lozenges could be the cure for the common cold, all double-blind, placebo-controlled data from these 15 double-blind, placebo-controlled clinical trials were used to determine relationships between iZn (or zinc) and reductions in durations of colds and to test for correlations and statistical significance. These tests utilized a Pearson correlation weighted by sample size analysis.

Using data from Table 1 to determine statistical results compiled in Table 2, lozenge iZn content correlated strongly with reductions in common cold duration with strong statistically significant and meaningful differences for both mean duration [r (14) = 0.84, $P < 0.001$] and median duration [r (13) = 0.73, $P = 0.004$] without the Smith et al. [40] outlier, while results with the Smith et al. [40] outlier were also statistically significant. Total daily lozenge iZn statistics were also strong and essentially identical to lozenge iZn statistics without the Smith et al. [40] outlier. From related Fig. 2a and b, nearly all of the zinc lozenges having "cure for common cold" potential can be seen to have had only one ligand (acetate or gluconate) and they had consequent high iZn content, while most failed lozenges had multiple ligands and consequent low or null iZn content. The average of the mean duration reductions (0 days) for the multi-ligand ZG and ZA lozenges differed significantly from the average of the mean duration reductions (3.37 days) of single ligand ZA and ZG lozenges ($P < 0.001$) and similarly for the averages (0.43 days vs. 2.9 days) of their median durations ($P < 0.001$) excluding the Smith et al. [40] outlier.

From Table 2, no statistically significant difference was observed for total zinc (iZn plus bound) and reductions in durations for either mean or median durations with or without the Smith et al. [40] outlier. These negative results for a search for a cure for common colds are also typical of results of reviews by others using a "head-count" system wherein the total number of negative zinc for colds reports (7 mean, 10 median) is compared with the total number of positive reports (8 mean, 4 median), which is a scientifically incorrect means of evaluating this data. Without solution chemistry computations to determine the amount of iZn in lozenges, this negative view is the dominant view in zinc lozenges for common cold research.

Reports using multi-ligand and non-ionizable zinc along with one report having lozenges with very low amounts of zinc and the ultra-bitter Smith et al. [40] outlier accounted for all instances of poor or null lozenge performance. From Table 3, five out of six formulations that had zinc compounds having a first stability constant K_1 of 1.7 or less succeeded, while only 2 out of 9 formulations that had zinc reaction products having higher K_1 values or that lacked solubility succeeded ($P < 0.02$), all being consistent with the in vitro observations of antirhinoviral activity only from iZn [2–10].

SPSS version 16.0 was used to calculate the weighted Pearson correlations. The significance values associated with those correlations was then calculated with the r to P calculator found at http://www.faculty.vassar.edu/lowry/tabs.html#r. Weighted correlation

Table 1
Effects of zinc on median and mean durations of common colds.

Trial year reference	N	Zinc compound	Zinc per lozenge (mg)	iZn per lozenge (mg)	Lozenges per day	Total daily zinc (mg)	% zinc as iZn	Total daily iZn (mg)	Reduction in median duration (days)	Reduction in mean duration (days)
Eby et al. [21]	65	ZG	23	16.56	9	207	72	149	4.8	7
Al-Nakib et al. [34]	12	ZG	23	16.56	9	207	72	149	n.a.	4.8
McCutcheon et al. [16]	49	ZP	24	0	9	216	0	0	0	0
Farr et al. [36]	77	ZG–C	23	0	8	184	0	0	n.a.	−1
Douglas et al. [22]	63	ZA–TB	10	0	6.4	60	0	0	n.a.	−4.4
Smith et al. [40]	110	ZG	23	16.56	9	207	72	149	0	0
Weisman et al. [41]	130	ZG	4.5	3.24	10	45	72	32.4	0	0
Godfrey et al. [42]	73	ZGG	23.7	2.60	8.1	192	11	21.1	n.a.	1.3
Mossad et al. [43]	99	ZGG	13.3	7.58	6	80	57	45.5	3.2	4.1
Macknin et al. [44]	249	ZGG	10.0	5.70	6	60	57	34.2	0	0
Petrus et al. [45] (non allergy)	55	ZA	9.0	9.0	9.9	72	100	89.1	n.a.	1.3
Petrus et al. [45] (allergy)	46	ZA	9.0	9.0	9.9	72	100	89.1	n.a.	4.1
Prasad et al. [46]	48	ZA	12.8	12.8	6.25	80	100	80	3.9	3.6
Turner et al. [47] (natural colds)	139	ZGG	13.3	7.58	6	80	57	45.5	−0.5	n.a.
Turner et al. [47] (induced colds)	136	ZGG	13.3	7.58	6	80	57	45.5	1	n.a.
Turner et al. [47] (natural colds)	143	ZA–SOP	5.0	0	6	30	0	0	−0.5	n.a.
Turner et al. [47] (induced colds)	133	ZA–SOP	5.0	0	6	30	0	0	0	n.a.
Turner et al. [47] (natural colds)	139	ZA–SOP	11.5	0	6	69	0	0	0	n.a.
Turner et al. [47] (induced colds)	137	ZA–SOP	11.5	0	6	69	0	0	0.25	n.a.
Eby and Halcomb [49]	75	ZO	37	0	9	333	0	0	0	0
Prasad et al. [11]	50	ZA	13.3	13.3	6.9	91.8	100	91.8	n.a.	3.1

Legend: ZA, zinc acetate; ZG, zinc gluconate; ZGG, zinc gluconate–glycine; ZG–C, zinc gluconate–citrate; ZA–SOP, zinc acetate–stearate–oleate–palmitate; ZA–TB, zinc acetate–tartarate–bicarbonate; ZP, zinc aspartate; ZO, zinc orotate.

Table 2
Statistical relationships of several measures of lozenge zinc on duration of common colds utilizing Pearson correlations weighted by sample size analysis.

	Statistics without Smith et al. [40] outlier	Statistics with Smith et al. [40] outlier
Lozenge iZn/mean duration	r (14) = 0.84, P < 0.001	r (15) = 0.62, P = 0.015
Lozenge iZn/median duration	r (13) = 0.73, P = 0.004	r (14) = 0.53, P = 0.050
Total daily lozenge iZn/mean duration	r (12) = 0.83, P = 0.001	r (13) = 0.48, P = 0.099, ns
Total daily lozenge iZn/median duration	r (13) = 0.77, P = 0.002	r (14) = 0.59, P = 0.027
Lozenge zinc (iZn + bound)/mean duration	r (14) = 0.12, P = 0.345, ns	r (15) = 0.08, P = 0.395, ns
Lozenge zinc (iZn + bound)/median duration	r (13) = 0.28, P = 0.282, ns	r (14) = 0.23, P = 0.219, ns
Total daily lozenge zinc (iZn + bound)/mean duration	r (13) = 0.14, P = 0.641, ns	r (14) = 0.10, P = 0.742, ns
Total daily lozenge zinc (iZn + bound)/median duration	r (13) = 0.26, P = 0.401, ns	r (14) = 0.19, P = 0.515, ns

Table 3
Relationship of zinc reaction products to efficacy.

Trial (year) reference	*N*	Zinc compound reported to be tested	Filler/excipients	Other ingredients	Zinc reaction products	First stability constant (K_1) of reaction product	Efficacy against common colds
Eby et al. [21]	65	Zinc gluconate	Dicalcium phosphate, microcrystalline cellulose, sodium starch glycolate	Magnesium stearate, coloring	Zinc gluconate	1.7	Yes
Al-Nakib et al. [34]	12	Zinc gluconate	Fructose	Methylcellulose, flavoring oil	Zinc gluconate	1.7	Yes
McCutcheon et al. [16]	49	Zinc aspartate	Sucrose, fructose	Calcium ascorbate, bee propolis, slippery elm, vitamin A palmitate, 2 stearates, Duratex™, spray-dried flavor oils,	Zinc aspartate	5.8	No
Farr et al. [36]	77	Zinc gluconate	Sugar, corn syrup	Citric acid, flavor oils	Zinc citrate	4.8	No
Douglas et al. [22]	63	Zinc acetate	Mannitol	Tartaric acid, sodium bicarbonate, flavor oils	Zinc tartarate	2.9	No
					Zinc carbonate	Not soluble	
					Zinc mannitol	n.a.	No
Smith et al. [40]	110	Zinc gluconate	Sucrose, fructose, sorbitol, mannitol	Mineral and acid stearates, Methocel®, pineapple powder and 3 spray-dried flavors	Zinc sorbitol and mannitol complexes	n.a	
Weisman et al. [41]	130	Zinc gluconate	Maltitol	Not stated	Zinc gluconate	1.7	No
Godfrey et al. [42]	73	Zinc gluconate	Sucrose, corn syrup	Glycine, flavor oils	Zinc glycinate	4.8	Yes
Mossad et al. [43]	99	Zinc gluconate	Sucrose, corn syrup	Glycine, flavor oils	Zinc glycinate	4.8	Yes
Macknin et al. [44]	249	Zinc gluconate	Sucrose, corn syrup	Glycine, flavor oils	Zinc glycinate	4.8	No
Petrus et al. [45]	101	Zinc acetate	Dextrose	Glycerol monostearate, stevia, peppermint oil, silica gel	Zinc acetate	1.0	Yes
Prasad et al. [46]	48	Zinc acetate	Dextrose	Glycerol monostearate, stevia, peppermint oil, silica gel	Zinc acetate	1.0	Yes
Turner et al. [47]	275	Zinc gluconate	Sucrose, glucose syrup	Glycine, flavor oils	Zinc glycinate	4.8	No
Turner et al. [47]	552	Zinc acetate	Sucrose, glucose syrup	Hydrogenated palm kernel oil, cotton seed oil, soy lecithin, Panoden™, flavoring and colors	Zinc stearate, zinc oleate, zinc palmitate	Not soluble	No
Eby and Halcomb [49]	75	Zinc orotate	Gum guar, cellulose	Silica, vegetable stearine	Zinc orotate	Essentially insoluble	No
Prasad et al. [11]	50	Zinc acetate	Sucrose, corn syrup	Cherry-flavoring oil	Zinc acetate	1.0	Yes

n.a. = data not available.

coefficients and the test-specific sample size were entered into the calculator to determine the significance level of the weighted correlation coefficient, given the sample size. Statistical significance in these correlations was declared when the two-sided P value was $\leqslant$0.050.

Indicating a cure for common colds, the hypothesis that there is a positive correlation between lozenge iZn content (both lozenge iZn and total daily iZn) and reduction in duration of common colds was confirmed by multiple measures with strong statistical significance and meaningfulness. Equally important, the hypothesis that there is no correlation between total (iZn plus bound) lozenge zinc and a cure for common colds was also confirmed.

The hypothesis that solution chemistry analysis at physiological pH 7.4 is the appropriate means of analysis was verified by implication from the highly significant dose–response statistical results for obtained.

Discussion

Take home message

Although strong iZn lozenges can cure the common cold, different formulations produce different results and only a few shorten colds sufficiently to be considered a viable cure for common colds. Ionized zinc (iZn) is the active ingredient in zinc lozenges and its consideration is vital for accurate review and interpretation of these clinical trials. Zinc lozenges shortened colds in a dose–re-

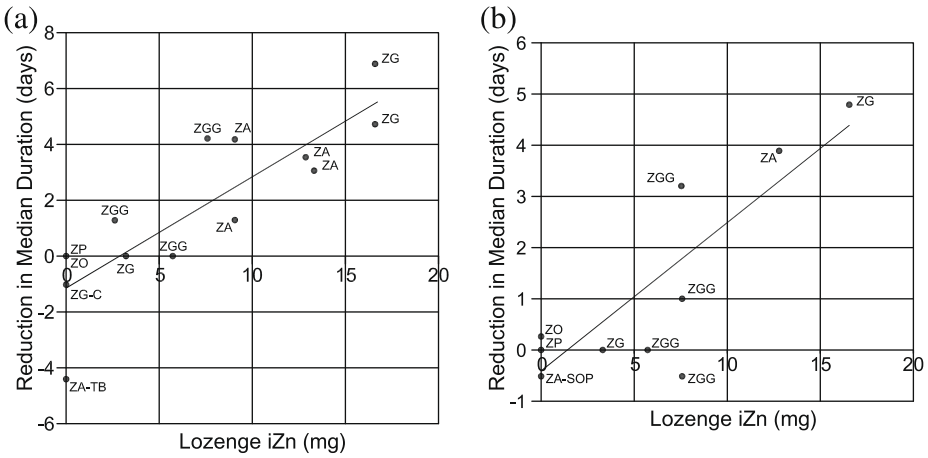

Fig. 2. (a) and (b) Mean and median duration of common colds treated with zinc lozenges.

sponse manner only when the active ingredient (iZn) measured at physiologic pH was considered. Results were statistically significant and highly meaningful by multiple measures, indicating a cure for common colds from strong lozenges. More clinical trials of high iZn zinc acetate lozenges are needed to confirm and extend these observations.

Sources of variance

Due to serious taste issues zinc gluconate was a poor choice for treating colds. Zinc gluconate forms extremely bitter complexes with all sweet carbohydrates except fructose, which resulted in bitterness-induced non-compliance and failure in several zinc gluconate lozenge trials, especially the Smith et al. [40] outlier. The overriding source of failure was requirement by pharmaceutical marketing companies for pleasant tasting, candy-like, non-metallic, non-astringent and non-drying zinc lozenges. Coupling taste requirements with exact placebo-matching [52] requirements resulted in testing multi-ligand, non-ionic zinc compositions that produced nearly all clinical failures. Further clinical tests of multi-ligand zinc lozenge compositions are strongly discouraged.

Fick's Second Law

Some failures could be attributed to infrequent treatment and rapid dissolution of lozenges since time of contact is required by Fick's Second Law of Membrane Diffusion [53]. For example, during the author's preclinical research in the early 1980s, the same highly effective zinc gluconate lozenges used in our 1984 clinical trial [21] did not appear effective when given at 3–4-h intervals. Since rhinoviral replication is extremely rapid [2], infrequent administration of iZn results in a loss of control over viral replication and produces clinical failures. Reduction in benefit when taking effective zinc lozenges less frequently than each 2 h is apparent to patients. Zinc lozenges used in future clinical trials should dissolve in the mouth in 20–30 min and not sooner for best efficacy.

Intranasal zinc

From the success of zinc lozenges, others hypothesized that intranasal iZn for colds would be effective and perhaps superior. We found that administration of 10 mM zinc gluconate (100× antirhinoviral concentration) nasal spray each 15 min was ineffective in shortening colds [49] even though our preclinical observations showed that it improved symptoms. Intranasal iZn treatment has been known to cause persistent to permanent anosmia upon contacting the olfactory bulb since 1938 and before, and its use has therefore been suggested to be unethical [49]. In 2009 the United States Food and Drug administration required discontinuation of zinc gluconate nasal gel for common colds due to anosmia risk.

Biophysics

The clinician would reasonably hypothesize that application of iZn to the nose would be preferable to throat lozenges, since rhinoviruses infect the nose and not the mouth. Consideration of the biophysics of the mouth–nose biologically closed electric circuit (BCEC) teaches a different view. The interior of the nose is positively charged electrically relative to the mouth (60–120 mV), and the nose repels positively charged substances including ionic zinc from nasal application [16–18,24,49]. This circuit is in addition to many other BCECs described by Nordenström [54], a member and chairman of the Nobel Assembly in Stockholm, Sweden. Had there not been a mouth–nose potential difference, intranasally applied iZn would likely have been shown effective in treating common colds as early as 1901 when intranasal ionizable zinc sulphocarbolate was reported as a treatment for nasal catarrh [55]. Franklin [56] in 1931 and Shields [57] in 1936 reversed this field using intranasal zinc ionization with ionic zinc being driven by an applied electrical voltage (3–5 mA) preventing allergies and common colds for a year with two 20-min zinc ionization office treatments. Wenner and Alexander in 1936 showed that the nasal mucosal tissues are temporarily damaged by zinc ionization [58]. To treat the nose with iZn for colds in the presence of this mouth–nose electrical flux is analogous to boarding a moving train at its destination.

Electrical resistances between the interior of the mouth and nose range from 1 to 500 kΩ. Low resistances are associated with frequent colds and nasal allergies, while high resistances are associated with immunity to respiratory viruses and lack of allergies [49]. Subjects with the highest mouth–nose electrical resistances are suggested to be identical to the 25% of the population that do not develop common colds when infected with rhinovirus [51]. Ionic zinc migrating from the mouth to the nose from zinc lozenges has been documented [59].

Magnesium and microbes

Although magnesium throat lozenges appeared effective in the rescue treatment of adult allergy-induced asthma, they greatly worsen and lengthen common colds and chronic sinusitis by increasing rhinoviral release, exponentially growing Candida albi-

cans and doubling herpes simplex growth [60]. In 1987 Geist et al. [61] at the University of Virginia School of Medicine conducted an in vitro antirhinoviral test of a number of ionic zinc compounds. In that study, the antirhinoviral effects of iZn were overwhelmed by the presence in the culture medium of 30 mmol magnesium chloride (over 30 times physiologic concentration), the exact concentration shown 20 years previously to be optimally effective in increasing rhinoviral cellular release from 8 to 310-fold [62,63]. Nine other antirhinovirus tests of ionic zinc compounds [2–10] did not include super-physiologic magnesium, and each showed strong antirhinovirus effects. Inclusion of magnesium in zinc lozenges (or placebos) for common colds would be expected – based upon the above – to greatly worsen common colds, worsen chronic rhinosinusitis and worsen herpes simplex-induced common colds. Hypothetically, throat lozenges containing ionizable magnesium might cause severe sequela including fatalities in rhinovirus-induced asthma, especially in children [64]. Swallowing magnesium dietary supplements would not cause these side effects since it would not increase intra-nasal or intra-lung magnesium concentration beyond normal physiological levels.

Zinc lozenge side effects

Zinc lozenge short-term use without magnesium is believed harmless [46]. Side effects have always been minor, and included taste disturbances (zinc gluconate mainly), and less frequently nausea, vomiting, dyspepsia and diarrhea. On rare occasions, elderly patients have experienced a noisome, bitter taste, suggesting an age-related zinc metabolism disorder [65]. Large amounts of zinc ingested for months can induce copper deficiency with consequent immune suppression and possible neurological disorders [66,67], while zinc acetate is used in the long-term treatment of Wilson's disease [68]. Ionizable zinc compounds are poorly absorbed in the gastrointestinal tract compared with zinc picolinate [69].

Caruso et al. report

The iZn active ingredient criteria for success presented herein appears immeasurably more important than the 11 superficial criteria used by Caruso et al. [70] in 2007 to claim – without any statistical evidence – that "the therapeutic effectiveness of zinc lozenges has yet to be established". To reach their negative conclusions about the efficacy of zinc lozenges against "naturally acquired colds", they ignored iZn active ingredient dose–response criteria. They omitted the highly authoritative British Medical Research Council Common Cold Unit positive trial [34] of ZG lozenges against induced HRV-2 colds, but included the negative report by Farr et al. [36] of ZG–C lozenges against induced HRV-13 and -39 colds demonstrating "cherry picking". They criticized our positive 1984 report [21] for failure to meet intent to treat analysis, yet our Discussion showed that if dropouts and those that did not return reports were hypothetically considered as negative responders, our positive results remained statistically sound ($P = 0.007$). They also criticized our 1984 report for failing to show similarity of groups at trial onset, ignoring our Table 1 "Characteristics of study groups" which showed successful randomization. They criticized all zinc lozenges for common cold trials for not having a demonstrable mechanism of action [the mandatory intercellular adhesion molecule-1 (ICAM-1) inhibition function] prior to the publication of the 2008 Prasad et al. [11] data showing ICAM-1 inhibition by iZn, and they did not consider the biophysical properties of the nose and mouth. They relied upon the faulty Geist et al. [61] negative in vitro assessment of the antiviral effects of iZn ignoring the 8 positive reports of the DuPont Pharmaceuticals team led by Bruce D. Korant, Ph.D. in their exhaustive 6-year study of the strong antiviral effects of iZn against nearly all rhinoviruses [2–9] and the confirming report by Merluzzi et al. [10] rejecting these conclusive positive reports as "a hypothesis". They failed to disclose the conflict-of-interest patents of one of the co-authors, Jack Merritt Gwaltney Jr., MD, to zinc nasal sprays for colds (US Patent Numbers 5,492,689, 5,422,097, 5,240,694).

Homeopathic formulations

Both zinc gluconate (*Zincum gluconicum*) and zinc acetate (*Zincum aceticum)* are listed in the Homœopathic Pharmacopœia of the United States. Consequently, a US Food and Drug Administration New Drug Application has not been required for zinc lozenges for common cold drugs having appropriate homeopathic labeling. Appropriate effective and pleasant tasting homeopathic formulations include:

- 2× *Zincum aceticum* in a base consisting of 70% agglomerated dextrose and 30% directly compressible fructose with glycerol monostearate lubricant and flavor oils plated onto silica gel for use in compressed tablets (7–9 tons compressive force), and
- 2× *Zincum aceticum* added late in a sucrose and corn syrup hard boiled candy with flavor oils.

Fructose, sucrose, dextrose, corn syrup and non-soluble ingredients do not normally react with zinc acetate [21,71]. Addition of other ingredients is not advised. Many fats will react adversely with zinc acetate at elevated temperatures eliminating iZn [49]. Using the mean duration trend line of Fig. 2a and a 2× homeopathic formulation lasting 20–30 min in the mouth and used each two wakeful hours during the first several days and as needed afterwards results in the following expected reductions in mean duration of colds using *Zincum aceticum* lozenges.

- 5 g lozenge – 18 mg iZn – 6.1 day reduction
- 4 g lozenge – 14.4 mg iZn – 4.6 day reduction
- 3 g lozenge – 10.8 mg iZn – 3.3 day reduction
- 2 g lozenge – 7.2 mg iZn – 1.7 day reduction
- 1 g lozenge – 3.6 mg iZn – 0.1 day reduction

By this analysis, only the lozenges having the highest iZn content (18 mg iZn) can reasonably be considered as a cure for common colds, while some smaller lozenges can be considered useful in shortening the duration of colds. These lozenges, if not adulterated, always produce a strongly astringent and drying mouth-feel, but they are sweet and pleasant tasting.

Tomato effect

Twenty-five years after the initial discovery by Eby [25], the concept of zinc lozenges as the cure for common colds remains a hypothesis. Lack of understanding of the physiological mechanism of many effective therapies by American physicians, especially nutrient-based therapies, has caused rejection of this discovery like previous rejections of other medical discoveries, which is called the "tomato effect". This notion refers to the erroneous fear of toxicity of tomatoes by American physicians in the 18th century since other plants in the nightshade family were highly toxic, even though Europeans commonly ate tomatoes at that time [72].

Denial

American medical experts have a long history of resisting scientific innovations from what they define as "the outside", referring to non-physician researchers [73]. The increasing economic and medical necessities for a viable common cold treatment should

outweigh these emotional responses to discovery. Even though medical doctors have taught for at least one hundred years that there is no cure for the common cold, strong iZn lozenges are hypothesized to be the cure for common colds.

Regulatory and efficacy concerns

Lack of regulatory review through use of homeopathic laws and dietary supplement regulations of the United States – even though throat lozenges are not allowed under the United States Dietary Supplement Health and Education Act of 1994 – has resulted in commercialization of zinc lozenges that are poorly effective to non-effective; and with additive magnesium, lozenges that might substantially worsen colds, adding credence to the notion that zinc lozenges do not cure colds. A 2008 cold-season market survey by this author of zinc lozenges found in national chain stores in Austin, Texas, USA, showed that none met the criteria of high iZn content and long dissolution times, and nearly all released zero iZn. Some zinc lozenges contained ZGG and from this analysis should slightly shorten colds (average of 1.8 days mean reduction), but their main benefit is hypothesized to be from a strong anti-histaminic action which would rapidly increase feeling of well-being. Most zinc lozenges also contained citric acid which slightly worsens colds (average of 1 day mean increase). Some zinc lozenges contained non-ionizable (at pH 7.4) zinc compounds including zinc oxide, aspartate, tartrate, picolinate, orotate and various amino acid chelates [74], which are believed inefficacious against colds [24]. Choices of zinc compounds that do not release iZn at pH 7.4 are believed predicated on commercial desires to avoid the orally astringent and drying nature of iZn, thus a cure for the common cold is precluded by marketing forces, not science. A current assessment of more than 40 over-the-counter zinc lozenges is maintained on the Internet [37]. Zinc lozenges marketed in the United States appear to compete based upon taste rather than efficacy.

Other respiratory benefits of iZn

Strong iZn (but not bound zinc) aqueous solutions are strong astringents having such low cell penetrability that action is essentially limited to cell surfaces and interstitial spaces. Permeability of cell membranes is reduced by iZn, but cells remain viable. Ionized zinc hardens the cement substance of capillary epithelium, inhibits pathologic transcapillary movement of plasma protein and reduces local edema, inflammation, and exudation. Additionally, iZn reduces mucus and other secretions in tissues containing goblet cells and other secretory cells, causing affected areas to become drier and heal faster [75].

Strong iZn lozenges have an immediate and beneficial effect on excess mucus production, throat congestion and nasal drainage due to allergies. Usual dosage is suggested to be one or two 18 mg iZn lozenges per day for treatment of allergy. These benefits result from the strong astringent action of super-physiologic iZn on cell membranes, especially mast cell and basophil cell-plasma membranes [14–16,76] resulting in temporary inhibition of all cellular and mast cell granule derived vasoactive agents including histamine, prostaglandins, leukotrienes, serotonin, bradykinins and cytokines. Although common cold symptoms are caused by viruses through bradykinins and cytokines, while allergy symptoms are caused by allergens through histamine and leukotrienes, concentrated iZn is beneficial in treating both conditions. These strong, natural, multiple anti-inflammatory effects help explain why iZn is beneficial in treating allergy [16], asthma [77], anaphylaxis [78], bronchitis [79] and croup [80]. Zinc also is mandatory for T-cell lymphocyte cell mediated immunity [81] giving further support for its role in treating viral infections generally.

Conclusions

In these 15 RCTs there was a strong, direct relationship between lozenge iZn content and efficacy, evincing a cure for common colds at the highest iZn content. The active ingredient in zinc lozenges was found to be iZn, while total zinc (iZn plus bound zinc) was not related to efficacy. Zinc lozenges slowly dissolving in the mouth over a 20–30 min period releasing adequate iZn (>18 mg) used each 2 h can shorten common colds by 6–7 days, which is a cure for common colds.

Literature reviews of zinc lozenge RCTs that do not fully consider the solution equilibrium chemistry and iZn content of zinc lozenges appear scientifically invalid. The 1987 in vitro assessment of antirhinoviral effects of zinc compounds that included unexplained super-physiologic magnesium chloride in the growth medium appears to have been at best an excessively stringent test and at worst a purposefully sabotaged test. Zinc lozenges must not contain ionizable magnesium since it can be expected to greatly worsen colds and exacerbate asthma, perhaps fatally. Of the 40 different brands of over-the-counter zinc lozenges and many variations of them currently available in the US, very few – based upon this analysis and ingredients listed on their labels – appear to release useful amounts of iZn regardless of total zinc content, and none of them can be considered as a cure for common colds. With several exceptions, nearly all appear likely to have a null effect on colds.

Consistent with the notion that a cure for common colds is exceedingly rare, only highly astringent and drying zinc acetate lozenges having 18 or more mg iZn described herein used each two wakeful hours are recommended as a safe and effective common cold cure. Additional high-dosage zinc acetate lozenge for common cold research is needed to confirm and extend these findings.

Conflict of interest statement

The author has expired patents concerning zinc lozenges for common colds, for example: US Patent 5,409,905 – Cure for Common Cold, and has profited from patent royalties and sales from http://www.coldcure.com.

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