The Common Cold

The "*common* cold" is appropriately named. It *is* the *most* "common" cause of acute illness, and the *most* "common" reason for health care visits [1]. Therefore physicians and other healthcare personnel must have good up-to-date information regarding the common cold and its most novel therapies.

More than 1 billion colds occur in the United States each year. Adults suffer from 2-4 colds per year, and children from 6-8 per year. Nearly 5% of the US population is suffering from a cold at any given time [2]. No wonder, it is the leading cause of missed days from school and work. And, no wonder, there are so many cold remedies on the market. One interesting remedy is zinc.

Zinc and the Common Cold Viruses

In the mid 1970s it was reported that zinc ions inhibit rhinovirus replication in vitro [3]. Several possible mechanisms have been observed: Zinc combines with the carboxyl termini of rhinovirus coat proteins, thus preventing the virus from combining with surface (ICAM-1) proteins on the respiratory epithelium [4]. Zinc prevents the formation of viral capsid proteins, thus inhibiting the replication of several viruses [3]. Zinc stabilizes cell membranes [5] and prevents histamine release [6]. Zinc potentiates the antiviral action of native human leukocyte interferon alpha ten-fold [7]. Zinc inhibits prostaglandin metabolism [8]. These antiviral observations suggest that zinc, if administered appropriately, may have a beneficial effect on the common cold. However, none of these activities of zinc have been demonstrated to occur at clinically achievable concentrations in humans.

Oral Zinc Lozenges

Numerous studies have examined the efficacy of zinc as an oral lozenge for the treatment of the common cold. This research has been conflicting; including studies that have agreed that zinc indeed has a beneficial effect, and those that have showed no effect. Meta-analyses by Jackson et al. published in 1997 and 2000 concluded that, 'Despite numerous randomized trials, the evidence for effectiveness of zinc salts lozenges in reducing the duration of common colds is still lacking' [9]. However, Eby has proposed an interesting hypothesis regarding 'zinc ion availability' (ZIA) and inactivation by certain additives as a resolution of the contradictory experimental results [10]. A recent (2004) meta-analysis of the zinc lozenge research by Eby revealed significant correlation between total daily zinc ion dosages and reductions in cold durations [11]. Another more recent review concluded that, 'Clinical trial data support the value of zinc in reducing the duration and severity of the common cold when administered within 24 hours of the onset of common cold symptoms' [12]. Given these new meta-analyses and Eby's 'Zinc Ion Availability' hypothesis, the data seem to suggest that zinc lozenges in the correct nonchelating formulation, with bioavailable ions, and with adequate zinc dosage, are capable of reducing the severity and duration of the common cold.

Intranasal Zinc: A Better Route

There is considerable evidence that the nasal cavity is the portal of entry and site of initial replication for most viruses that cause the common cold [13]. The site of rhinovirus replication is the nasal mucosa [14,15], and these infections are more readily initiated by intranasal than intraoral inoculation of virus [16-18]. Zinc lozenges do not effectively deliver zinc to the nasal mucosa [19]. It is logical to assume that any affect that zinc may have on cold viruses would be optimized by direct intranasal administration. This paper will review the published research dealing with intranasal zinc administration as a treatment for the common cold.

The Research

The first published study on intranasal zinc and the common cold was published in 2000 by Michael Hirt et al. [20]. This study attempted to reproduce the encouraging results of a preliminary study by C.B. Hensley, PhD, and R. Davidson, PhD that showed an 85% reduction in the duration of cold symptoms (unpublished data, 1999). Their reported result was that the administration of intranasal zinc gluconate emulsion reduced the duration of common cold symptoms by 75%, from 9.0 to 2.3 days ($p<0.05$). The researchers selected for subjects with relatively severe natural colds by requiring the subjects to have had at least 3 different symptoms within the first 24 hours of illness. They effectively pioneered the experimental *standard dosing/preparation**. Their endpoint was complete resolution of symptoms, determined by patient diary entries. The main problem was that their blinding process was not evaluated.

* The *standard dosing/preparation* consists of 33mM zinc gluconate in an emulsification of benzalkonium chloride, glycerine, hydroxymethylcellulose, sodium chloride, and sodium hydroxide (pH 7.2). The placebo is an identical preparation with the exception of the omission of the zinc gluconate. Study medications are administered as a single nasal spray of 120 uL per nostril, 4 times each day (R. Turner [22]= 5 times/day), at 4-hour intervals. The total daily dose of elemental zinc is about 2.1 mg per day.

The subsequent study by Belongia et al. in 2001 was unlike the other three studies, given that a very different zinc preparation was used [21]. The active medication was a preparation containing 0.12% zinc sulfate heptahydrate in benzalkonium chloride, benzyl alcohol, sodium chloride, and water. Each inhalation delivered 0.1 mL spray, giving a dose of 0.011 mg elemental zinc per dose (4 inhalations), four times per day. The total maximum daily dose was 0.044 mg elemental zinc. This was much less than the ~2.1 mg/day that was delivered in the other three studies by the *standard dosing/preparation**. This extremely low dose alone could explain the relative lack of observed effect. The researchers did report a significantly lower symptom score in the patient diaries of the treatment group on the day after enrollment, but this effect was not seen on any other day, and was considered trivial.

The experiment by Turner, also published in 2001, was different from the others in that he only evaluated intranasal zinc effects on experimentally induced rhinovirus colds [22]. The administration of the study formulations, *standard dosing/preparation** and placebo (5 instead of 4 doses/day), was started 3 days prior to RV23 or RV39 virus challenge. The prophylaxis and treatment with intranasal zinc gluconate had no significant effect on either the infection rate or severity of the rhinovirus colds. No significant difference was observed in the symptom diaries; however the statistical power of the study has been questioned [25]. This study also performed daily nasal lavages following virus inoculation to measure zinc concentration and to quantitate virus shedding. Mean zinc concentration in the nasal lavage was ~0.07mM. Turner assumes a further dilution (1:10) by inoculation into cells, and argues that such a low concentration of zinc would be 'unlikely to affect virus replication.' Zinc has been shown to inhibit the replication of rhinovirus, in vitro, at concentrations of 0.03-0.1mM [26]. However, Turner also notes: 'Quantitation of virus in nasal lavage of the volunteers challenged with RV39 revealed a significant effect of zinc treatment on the amount of virus shed on days 1 and 2 after virus challenge.' Turner saw this observation as suggestive evidence of an antiviral effect of zinc; but the lack of a clinically observed reduction in either incidence or severity of infection overshadowed this finding. This study was limited to studying experimentally induced rhinovirus colds. The antiviral effects of zinc and the potential hypotheses on the mechanism of action have been demonstrated on rhinovirus. However, the vast majority of colds are not caused by rhinovirus. Furthermore, clinical symptomatic improvement seen in the other studies may be a result of zinc's affects on other natural cold-causing pathogens.

The most recent study was done in 2003 by S.B. Mossad [23]. This study was very similar to the original study by Hirt et al. [20], but improved upon it somewhat by documenting microbiological information, onset of perceived improvement, severity of individual symptoms, season of year, and blinding process. Mossad observed a slightly less drastic effect than Hirt et al. A difference in the two studies that might help to explain the slight variation in results: Hirt et al. only enrolled subjects whose symptoms had been manifest for 24 hours or less, whereas Mossad excluded subjects with symptoms manifest for less than 24 hours. Therefore Mossad may have selected for subjects with better-established illnesses. Nevertheless, the results showed a significantly shorter time to cold resolution (no symptoms) in the zinc group (4.3 days) compared to the placebo group (6 days) ($p=0.002$). Days to resolution of all but any one common cold symptom were also significantly shorter in the zinc group ($p=0.006$). Eighteen of the 78 patients (23%) had rhinovirus identified by PCR ($p=0.29$). The median time to rhinovirus cold resolution was also shorter: zinc treatment= 3 days, placebo= 6 days ($p=0.02$). The most prominent symptoms of the common cold, including nasal drainage, nasal congestion, and sore throat, were the symptoms that were most affected. This study's methodologies were quite sound and the results agree with the previous study by M. Hirt [20].

In an attempt to monitor a treatment effect, all four of the studies used symptom diaries with modified numeric (0-3) or (0-4) severity scales for each common cold symptom based on criteria developed and validated by Jackson et al. [24].

Summary

Four randomized, double blind, placebo-controlled experiments have studied the effects of intranasal zinc administration on the common cold [20-23]. Two studies that were similar in methodologies, using the same *standard dosing/preparation** of zinc gluconate emulsion on naturally occurring colds, showed a beneficial effect [20,23]. One study that used an atypically small concentration and dose of zinc sulfate in a spray showed a small, potentially insignificant effect [21]. And one study that specifically only studied experimentally induced rhinovirus colds, using approximately the *standard dosing/preparation** of zinc gluconate emulsion, suggested a small antiviral effect, but showed no clinical effect [22]. The disparities in methodologies such as different dosages and different types of colds/viruses (naturally occurring versus experimentally induced rhinovirus) may explain the discrepancies in the reported results.

Anosmia From Intranasal Zinc

Records documenting the association of intranasal zinc and anosmia (loss of smell) date back to the 1930's. Canadian researchers experimented with the intranasal application of zinc sulfate for polio prevention and noted that about 15% of the children treated developed anosmia that lasted for months [27]. Zinc has also been successfully used to produce anosmia in laboratory animals [28].

Recently there have been at least eleven case studies that have documented anosmia resulting from the intranasal application of zinc gluconate for the common cold, along with a number of lawsuits consequent to this phenomenon. This sporadic side-effect appears to be long lasting or permanent in some cases, as evidenced by the case report of unchanged hyposomnia persisting beyond 23 months. Suggested mechanisms include direct olfactory toxicity or blockage of the nonspecific cyclic nucleotide-gated channel needed for depolarization of these olfactory cells. [29]

Conclusion

The current evidence suggests that intranasal zinc gluconate in the *standard dosing/preparation** does reduce the duration of naturally occurring colds [20,23]. Other contradictory studies have been flawed with inadequately small doses of zinc [21] and limitations due to unrealistic laboratory induced rhinovirus-only-caused colds [22].

More studies, in a broader population, comparing zinc nasal gel with other cold remedies (such as decongestants, antihistamines, antitussives, and antipyretics/analgesics) are needed before recommending it as first-line therapy. Furthermore, the occurrence of anosmia from intranasal zinc must be studied to determine the extent of this risk and the duration of this effect. Once determined, the public must be informed of this potential risk.

Do you want to risk your sense of smell in order to get rid of your cold sooner?

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