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Failure of Effervescent Zinc Acetate Lozenges To Alter the Course of Upper Respiratory Tract Infections in Australian Adults

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Effervescent lozenges containing 10 mg of zinc acetate were evaluated as a treatment of upper respiratory tract infections in a double-blind randomized trial by using a placebo which was indistinguishable to most observers in taste and appearance from the active material. Of the 70 treatment courses used by 55 individuals in 34 families, 63 (33 zinc and 30 placebo) were considered evaluable, in that the volunteer used the medication at least four times daily for at least 3 days, the average utilization being 5.4 days at an average dose of six lozenges daily. Six users of zinc reported nausea (versus no placebo users), and eight reported an unpleasant taste or aftertaste (versus one placebo user). No benefit was observed among the users of zinc acetate. The mean duration of symptoms in users of the zinc was 12.1 days, compared with 7.7 days in those who used the placebo. Nor was any beneficial effect of zinc evident among the four zinc-treated versus the two placebo-treated individuals from whom rhinovirus was grown.

This study was prompted by the report by Eby et al. (4), which suggested that zinc gluconate lozenges could abort the symptoms of common upper respiratory tract infections. In that study, 23-mg zinc gluconate lozenges were sucked up to eight times daily following the onset of upper respiratory tract symptoms. The placebo lozenges were apparently easily distinguishable from the active ones. The differences recorded in the duration of illness between those who used placebo and those who used active lozenges were highly significant.

The present study was begun on the assumption that if the findings of Eby and co-workers could be replicated by other investigators, the desirability of reducing the dose of zinc and of performing the study under truly double-blind circumstances would have a high priority. Fauldings Ltd. prepared effervescent lozenges of zinc acetate, each containing 10 mg of elemental zinc, and a placebo which contained sodium acetate.

MATERIALS AND METHODS

Placebo matching study. As a test of the adequacy of the placebo, 20 specially recruited volunteers were invited to identify each of a randomly assigned block of four tablets—two zinc and two placebo—and to record their findings after allowing each of the tablets to effervesce in their mouths for 2 min. The tests were done 1 h apart, and each tablet remnant was retained for further checking if desired.

Treatment study. All of the participants in the main trial were healthy adults who had in the previous year participated in a study of intranasal interferon prophylaxis against rhinovirus infections (3). In that study, they maintained throughout the winter diary records of respiratory symptomatology and cooperated in a complex study protocol which called for initiation of prophylaxis when another member of the family developed a cold. For the present study, the manufacturers provided 150 sequentially numbered bottles, each of which contained 48 effervescent tablets of either zinc acetate or placebo randomly allocated to the sequence. Each of 99 individuals from 37 families was provided with a bottle of tablets in April 1985 and instructed in the present protocol. Informed consent, which included a description of the early study and full discussion of the purpose of the present study, including the hypothesis that zinc was the active agent, was obtained, and procedures were approved by the University of Adelaide Ethics Committee. For each family, one individual was appointed to supervise the maintenance of symptom diaries and to maintain regular weekly contact with the study supervisor. The protocol required that when a participating individual developed two respiratory symptoms for 1 day or one respiratory symptom for 2 days, he or she reported at once to the nurse at the office of his or her general practitioner, nasal and pharyngeal swabs were collected for viral study, and medication from the bottle assigned to that individual was commenced immediately. The lozenge was to be slowly dissolved in the mouth, a process which took about 10 min. The study office was notified, and the instructions required that each treated individual use from six to eight lozenges at about 2-h intervals each day for a minimum of 3 days and for up to 6 days if symptoms continued. At 2 weeks after therapy commenced, a home visit was made, at which time all leftover tablets were collected and a new bottle of medication was left in the event of further cold symptoms developing. A questionnaire relating to the respiratory episode and to the acceptability of the lozenge was also completed at this time. It was a double-blind study and all observers remained blind to the identity of the treatment courses until all data were collected. For the first 30 cases, the code was broken in July, and for the entire study, it was broken in November.

Datum analysis. Datum analysis was by treatment course. The study design meant that an individual could use more than one treatment course and that the identity of the treatment course he used could be different from one course to the next. In Table 1, the characteristics of a user are counted once for each course he or she used of the medication under consideration. In comparing the duration of episodes, symptom diaries were analyzed and an episode ran from the onset of nasal, throat, or cough symptoms to the last consecutive day on which such symptoms were re-

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TABLE 1. Data on evaluable courses of zinc and placebo

Characteristic	Value for group	
	Zinc	Placebo
No. of different users	30	28
No. of courses used	33	30
Mean age (yr)	30.7	35.6
% Female	58	50
% Smokers	28	21
% Hay fever	31	21
Mean no. of respiratory episodes for 6 mo in 1984	3.3	2.6
Mean no. of days of respiratory symptoms for 6 mo in 1984	33.5	27.5
No. of users with >2 days of symptoms before treatment	1	1
No. of users with >1 day of symptoms before treatment	10	6
Mean no. of tablets used per course	35	30
Mean no. of days of medication per course	5.4	5.3
Mean no. of tablets per day	6.4	5.7
Viral cultures		
None collected	2	1
No. collected on days 1 and 2 of illness	24	22
No. collected on days 3 and 4 of illness	7	7
Rhinovirus cultured (no. of episodes)	4	2
Other virus cultured (no. of episodes)	1 (Adenovirus)	2 (1 Influenza A, 1 RSV)[a]

[a] RSV, Respiratory syncytial virus.

corded. For each symptom, a score was derived from the diary, as the user had been asked to classify each symptom as mild (1 point), moderate (2 points), or severe (3 points), so that 2 days of moderate nasal symptoms and 1 day of severe nasal symptoms would incur a nasal score for that episode of 7. (Mean days of symptoms and mean symptom scores were compared by the Student *t* test.)

At the end of the study, all used medication bottles were collected and the remaining contents, both of used and unused bottles, were checked. The number of tablets consumed was checked against the estimate by the patient of consumption. When discrepancies occurred, the preferred figure was that derived from tablets left over.

RESULTS

Placebo adequacy. In the evaluation of distinguishability between placebo and zinc lozenges, 9 of 20 volunteers correctly identified differences in the two pairs of lozenges, but only 5 of the 9 correctly identified zinc from placebo; the remaining 4 said the zinc was placebo and vice versa. We estimate that the probability that 5 or more of 20 volunteers would correctly assign the four tablets on chance alone is 0.10.

Participants. A total of 70 treatment courses were used by a total of 55 individuals in 34 families; 13 individuals used 2 courses, and 2 individuals used 3 courses. Of the 11 individuals who used two courses, 3 used two courses of zinc and 8 used one course each of placebo and zinc. Both individuals who used three treatment courses used two courses of placebo and one of zinc. Of the treatment courses, 35 were zinc and 35 were placebo. We excluded from the analysis treatment courses in which the residual tablet counts indicated that the individual had not used the tablets at least for 3 days and at the rate of 4 or more per day. Using these criteria, seven courses were excluded as unevaluable (two zinc and five placebo recipients). The two zinc recipients used no lozenges and six lozenges, and the cold symptoms lasted 3 and 25 days, respectively. The five placebo recipients used 5, 10, 14, 8, and 12 lozenges, and their symptoms lasted, respectively, 3, 7, 7, 45, and 6 days. A total of 30 individuals used 33 evaluable courses of zinc, and 28 individuals used 30 evaluable courses of placebo. Those who used zinc were slightly more likely to be female, to smoke, and to have histories of hay fever. The zinc users also had slightly more severe experiences of respiratory infections during the 6 months of the previous interferon study in 1984 (Table 1).

On average, the zinc users used 35 tablets per course, compared with 30 for the placebo group. The durations of medication in the two groups were similar, the difference in tablet consumption being a result of the fact that the zinc users used more tablets per day. Generally, however, despite these minor differences, the comparibility of the two treatment groups was acceptable. Viral cultures were collected for all but two of the zinc-treated episodes and all but one of the placebo-treated episodes; 5 of the 31 cultured zinc-treated cases grew viruses (16%), compared with 4 of the 29 placebo-treated cases (13.8%).

Illness impact. The mean durations of illness and symptoms in the two groups as documented in the daily diary maintained on all medication users are presented in Table 2. Whereas 60% of the placebo-treated cases lasted 7 days or less, only 42% of the zinc-treated cases did so, and 24% of the zinc-treated cases versus 13% of the placebo-treated cases lasted more than 12 days. Both rhinovirus cases in the placebo group reported duration as 5 days, compared with 5, 8, 9, and 53 days for those treated with zinc. Symptomatology in the two groups was also examined according to whether it involved nasal, throat, cough, or systemic symptoms, and each was assigned a severity score for each day. No consistent or significant differences emerged. Using a classification of the episodes into doubtful, uncertain, and definite respiratory illnesses by criteria which we have used in previous studies (2), we found no evidence that the use of zinc resulted in less severe syndromes (Table 2).

Tablet acceptability. A questionnaire about medication side effects was given to all users of the medication shortly

TABLE 2. Characteristics of respiratory episodes among evaluable cases in the two treatment groups

Characteristic	Value for group		Significance (Student *t* test)
	Zinc	Placebo	
No. of courses	33	30	
Mean no. of days of symptoms			
Respiratory	12.1	7.7	0.08
Nasal	8.5	6.3	0.3
Throat	3.9	4.0	0.97
Cough	7.0	3.8	0.1
Systemic	2.4	2.9	0.6
Mean score (points)[a]			
Nasal	11.7	9.8	0.5
Throat	6.1	6.2	0.96
Cough	10.6	6.3	0.2
Episode classification (no.)			
Doubtful	0	1	
Uncertain	7	9	
Definite	26	20	

[a] For scoring system, see Materials and Methods.

after the completion of the study and before the code was broken. Five volunteers failed to complete the questionnaire. Of 30 zinc users, 8, compared with 1 of 28 placebo users, reported that the medication had an unpleasant taste, and 5 of those who used zinc also complained of an unpleasant aftertaste. For neither group was mouth irritation a significant problem (four reports of slight irritation in each group). Only with zinc were 6 volunteers troubled by mild nausea. Of these 6 complainants, 4 also claimed that the zinc had an unpleasant taste. The volunteers were also asked to judge subjectively whether the lozenges made a difference in their cold symptoms, and 12 zinc and 7 placebo users claimed that the tablets had resulted in a shorter, milder illness than they expected. In each group, 20 respondents said they would be quite happy to use this medication for future colds.

DISCUSSION

The only previous study in which zinc lozenges were used to treat undifferentiated acute respiratory infections reported a mean reduction in symptom duration of 7 days for those who used the active material; the study was comparable in size to our study (4). Our conclusions are quite different. The American study differed in a number of ways from our study. Volunteers in the American study were recruited through the media and commenced therapy only after recruitment. The placebo was easily distinguishable from the active agent, which caused a greater incidence of side effects than there were in our study. The dose of elemental zinc used in the previous study was 23 mg per lozenge, compared with 10 mg in the present study, and the salt they used was gluconate, compared with acetate in our study. In the American study, an original study population of 146 was reduced to 65 through lack of compliance and exclusions made postrandomization. Nevertheless, the difference reported in illness duration and severity by those who used the active material was very convincing.

Like Eby and co-workers, we studied undifferentiated upper respiratory illnesses, and the causative agents could have been different in the two studies. Viral agents were implicated in only 9 of the 63 (14%) evaluable cases which were cultured in our study. This rate is consistent with our rates of viral isolation in studies of community-acquired upper respiratory illness in Adelaide adults during the previous 2 years (2, 3). Some strains of rhinovirus are susceptible to zinc ions incorporated in tissue culture preparations (5). We demonstrated no evidence, however, that the patients from which rhinovirus was isolated had benefited.

Our zinc users, however, used, on average, 350 mg of zinc acetate over the 5 days of their usage, which is at least four times the recommended daily allowance of zinc. We cannot be sure from the study by Eby and co-workers how much zinc the volunteers actually ingested. An effervescent lozenge, which caused considerable fizzing in the mouth during its dissolution over a period of 10 min, seemed an ideal vehicle to ensure that the zinc was widely disseminated in the oral and pharyngeal mucosa.

As in the study by Eby and colleagues, our volunteers were fully informed as to the study hypotheses and the nature of the hypothesized active agent. Although in our study there was some difference between the two groups in terms of side effects, we performed a genuinely double-blind study, and there was excellent compliance. Our tests of distinguishability of the two lozenges lead us to believe that this factor did not influence our results.

Both zinc and placebo lozenges were generally acceptable, but the zinc preparation was less so, causing nausea in 20% of its users and an unpleasant aftertaste in 16%. However, zinc acetate in our study has exerted no beneficial effects on its users, compared with those who used the placebo. This is in spite of the fact that power calculations indicate that the study had 85% power to demonstrate a difference between the two groups as large as that reported by Eby and co-workers.

At this stage, the case for zinc lozenges in the treatment of upper respiratory illness seems unproven. Further evidence in support of this approach to this major public health problem is required before the approach can be advocated as a part of clinical management.

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