Zinc gluconate lozenges for common cold

A double-blind clinical trial

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ABSTRACT

Weismann K, Jakobsen JP, Weismann JE, Hammer UM, Nyholm SM, Hansen B, Lomholt KE, Schmidt K. Zinc gluconate lozenges for common cold. A double-blind clinical trial.

Dan Med Bull 1990; 37: 279-81.

In a double-blind clinical trial, a total of 463 volunteers were enrolled in a study designed to compare the effects of zinc gluconate lozenges (4.5 mg zinc) and a placebo for common cold. The tablets were to be taken every 1-1½ waking hours at the first symptoms and for the following days until the common cold was over, but for no longer than 10 days. During the winter months of 1987 and 1988, 145 experienced a common cold and 130 completed the study. For final analysis, 61 patients in the zinc lozenge group and 69 patients in the placebo lozenge group were evaluated (Table 1). Based on the patients' records the duration and severity of the common cold were compared (Figs. 1, 2a and b). No statistically significant differences were found between the patient groups. Two recent studies using a five-time higher zinc dose per lozenge for common cold showed a significant, positive effect, but associated with frequent side-effects, first of all taste distortion. In the present study there was a weak tendency (not statistically significant, p=0.12) towards more patients in the zinc lozenge group than in the placebo lozenge group reporting side-effects.

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INTRODUCTION

Viral upper respiratory infections in the form of common colds are a frequent cause of acute illness and are responsible for a significant proportion of lost school days and work days. In the United States, it has been estimated that common colds cost some 2.5 billion dollars per year (1). The management of common cold includes use of a variety of remedies which are believed to minimize the primary symptoms of common cold (nasal drainage and nasal congestion) as well as the accompanying secondary symptoms (headache, fever, myalgia, sneezing, sore throat, hoarseness and coughing). No effective drugs or immunization therapy against the rhinovirus group has yet been found, but zinc lozenges recently were reported to have an effect (2. 3). Zinc ions are known to inhibit rhinovirus replication *in vitro* at concentrations about 0.1 mM, about ten times the normal serum or plasma zinc concentration (4). The reports prompted us to perform a clinical study with low-dose zinc gluconate lozenges for common cold in a Danish population.

MATERIAL AND METHODS

Patients

The study was designed as a prospective double-blind clinical trial with zinc gluconate lozenges of 4.5 mg zinc to be compared with placebo lozenges for common cold. Patients 18-65 years old who were known to suffer from common cold during the cold season were invited to participate in the study. Pregnant, lactating women and patients with diabetes mellitus were not included. After giving their informed consent, the patients recieved written information about the study, instructing them to start therapy immediately after the first symptoms of common cold appeared. The lozenges were to be taken every 1 to 1½ waking hours, in all 10 lozenges daily for a maximum of 10 days. A diary was to be kept daily stating the approximate hour when each lozenge was taken. At the start of the study, the patients registered the following symptoms: indisposition, headache, fever, muscle pain, running nose, nasal congestion, sore throat, coughing and hoarseness. A schedule indicating many, some, or no symptoms was filled out. During the following days, the patients were instructed to note their overall condition every evening by putting a cross on a 11 cm horizontal line with »well-being« at the left, »not quite well« in the middle and »extremely bad« at the right. The length of the marked line, the VAS (visual analogue scale) score in mm was taken as an estimate of the disease severity (5).

Side-effects were noted and specified in the diary. Ten days after the start of the trial, all patients were to consult their physician who made a record of the course of the disease, and the diary and remaining tablets were delivered. Six general practitioners residing in the suburban area of Copenhagen conducted the study which was approved by the local ethics committee for medical research.

Medication

Preliminary studies had shown us that treatment with lozenges with a 3.5 mg zinc content resulted in saliva zinc levels ranging from about 60 to 250 µmol/l. With a 7.5 zinc content per lozenge, the saliva concentration ranged from about 1,400 to 4,400 µmol/l, well above the intended level of 0.1 mM/l, but produced an unbearable metallic taste in the volunteers. Therefore, we decided on a zinc dose of 4.5 mg per lozenge which was generally well tolerated. The medication did not produce significant changes in the serum zinc levels when given 12 times daily for seven days to nine patients. The zinc and placebo lozenges consisted of maltitol syrup with natural flavours. The active lozenges contained 31.3 mg zinc gluconate (=4.5 mg zinc). The daily medication was 10 lozenges, corresponding to 45 mg elemental zinc. This is three times the recommended daily allowance for zinc (15 mg). No other drugs for common cold were allowed during the study.

Statistics

The duration in days of the common cold was evaluated by survival analysis using the Mantel-Cox test with cessation of symptoms as end-point.

The severity of the disease in the two groups during the trial was analysed by comparing the mean and median VAS score in mm for each day the patient remained ill (Mann-Whitney test) (5).

Differences between the two groups with respect to patient characteristics (sex, age, smoker or non-smoker) were tested by exact test in unordered (r × c) contingency tables.

RESULTS

A total of 463 patients were primarily enrolled in the study which ran over two periods (1 February 1987-15 April 1987 and 1 September 1987-1 Februar 1988), during which a common cold was experienced by a total of 145 patients, of whom 130 completed the trial. Sixty-nine patients received placebo and 61 received zinc (Table 1).

No statistically significant difference at 5% level between the two groups with regard to sex, age, smoking or severity of symptoms

Table 1. *Number of allocated patients.*

Patient status	Placebo lozenges	Zinc gluconate lozenges	Total
Entering the trial	77	68	145
Excluded because of lacking records	8	6	14
Excluded because of too low age	0	1	1
Not started treatment	154	164	318
No. of patients for final evaluation	69	61	130

Table 2. *Side-effects in patients treated with placebo and zinc gluconate lozenges.*

Side-effects	Placebo lozenges	Zinc gluconate lozenges
Yes	15	21
No	54	40
Total	69	61

(p=0.12)

at the start of the study was present. There was no statistically significant difference between treatment groups with respect to the frequency of patients who did not experience a cold and hence did not participate in the study (cf. Table 1).

The *duration* of common cold was virtually identical in the zinc and placebo treated groups (Fig. 1). As seen from the figure, the two curves had an almost parallel course during the first five days. From day six onwards, the placebo group was somewhat lower than the zinc group, stressing that zinc did not shorten the duration of the disease.

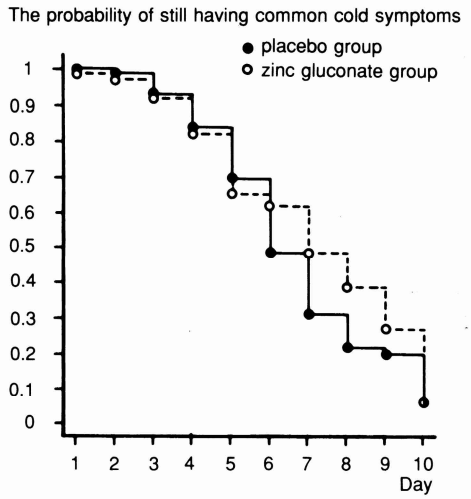

Fig. 1. *Survival curves showing duration of common cold in zinc gluconate (n=61) and placebo treated patients (n=69).*

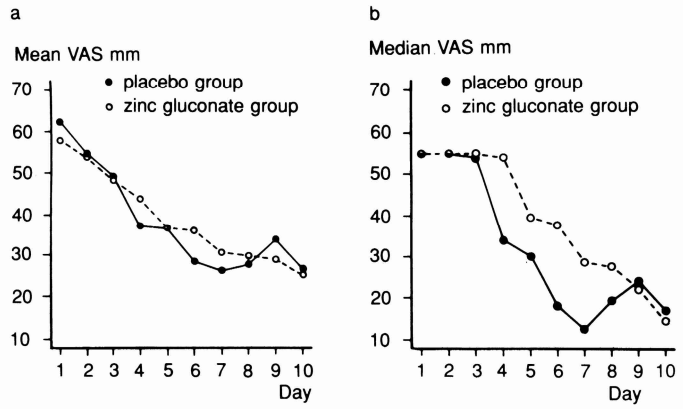

Fig. 2a and b. *Disease activity in zinc gluconate (n=61) and placebo treated patients (n=69) with common cold expressed as visual analogue scale (VAS) score in mm, a: mean values, b: median values.*

The *severity* of common cold symptoms is seen from Figs. 2a and b. The mean VAS curves of the two groups did not differ much (Fig. 2a). No statistically significant difference at day six (the day with largest difference) was found by Mann-Whitney test (p=0.14). Among the five days with the greatest difference between the groups (days 1, 4, 6, 7, and 9), the placebo curve was the lower on three days (4, 6 and 7) and the higher on two days (1 and 9), which also indicates lack of any difference between the two treatments.

When the median VAS curves were plotted (Fig. 2b), the placebo group was lower than the zinc group from day four to eight, but not statistically different at 5% level. The difference between figs. 2a and b is mainly due to two patients in the placebo group who had high VAS scores above 90 mm. The patients were asked to compare the course of the actual common cold with prior episodes. No statistically significant difference in the opinion of the two groups was found (p=0.64). The number of tablets taken during the study was not statistically significantly different in the two groups on any day (Mann-Whitney test, p>0.05).

Side-effects

Among the 130 patients who completed the study, 50 (38%) reported side-effects. A revision of the complaints showed that seven patients of each group had recorded symptoms which were related to the common cold (sore throat, cough and headache). Among the remaining 36 patients, 21 on zinc and 15 on placebo had various complaints, but there was no statistically significant difference between the groups (Table 2) (p=0.12). The complaints included dry mouth, dizziness, sleepiness, stomach symptoms and taste distortion. It was found that 3/61 patients (5%) on zinc lozenges complained of an unpleasant metallic taste. No patients on placebo experienced this. In no case did side-effects cause discontinuation of therapy.

DISCUSSION

The present study failed to show a beneficial effect of lozenges with zinc gluconate on the duration or the severity of common cold. *Eby et al* (2) performed a successful double-blind study of zinc gluconate lozenges for common cold. The patients received either lozenges containing 23 mg zinc or placebo lozenges every two waking hour after an initial double dose. After seven days, 86% of 37 zinc-treated patients were asymptomatic compared with 46% of 28 placebo-treated patients which was significantly different. As in the present study, the effect was evaluated by the patients' records of symptoms. Estimates of the duration of common cold were based on exponential decay curves and were found to average 3.9 days and 10.8 days in the zinc and placebo treated groups, respectively. The initial total severity score was lower in the zinc group 8.7±0.7 (mean±SEM) than in the placebo group score of 10.5±0.7, which makes it difficult to assess at what time the two plots became convincingly different (2).

We chose a zinc dose of 4.5 mg per unit because pilot studies had shown us that higher zinc doses are unacceptable to most persons. A pronounced metallic taste distortion is a particular complaint when the zinc content per unit exceeds 7.5 mg. In the study of *Eby et al* (2), 54% of the patients receiving 23 mg zinc lozenges reported side-effects, compared with 18% in the placebo group. Among 11 drop-outs on zinc gluconate, the cause was side-effects in seven patients while this was the case in only one of five drop-outs in the placebo group. Another recent study has shown favourable results of zinc gluconte lozenges for rhinovirus colds (3). In a prophylaxis study 29 patients received zinc gluconate lozenges (23mg) and placebo lozenges for two days before challenge with an infecting dose of *Human rhinovirus 2.* Zinc reduced the total mean clinical score from 8.2 to 5.7 as compared with the placebo treated group. In a therapeutic study, 69 volunteers were inoculated with *Human rhinovirus 2,* and those who developed cold symptoms were randomly allocated to either zinc gluconate or matched placebo

lozenges every two hours they were awake. Zinc reduced the mean daily clinical score, and this was statistically significant on days four and five, but there was no effect on the rate or amount of virus excreted by the patients. This is an intriguing result since zinc is believed to work by inhibiting virus replication. Side-effects were not mentioned.

The success of a cure for a transient disease such as common cold depends on patient compliance. If side-effects outweigh the potential beneficial effects of therapy many patients will prefer to await spontaneous cure. Our low-dosage zinc therapy was well tolerated but ineffective in abating common cold. Alternative ways of administration of zinc than in lozenge form might be considered. Furthermore, studies dealing with a possible mechanism of action of zinc in rhinovirus infection should be undertaken.

Acknowledgement: This study was conducted in cooperation with *Kirsten B. Stæhr*, A/S Alfred Benzon, Helseholmen 1, DK-2650 Hvidovre. The zinc gluconate and placebo lozenges were manufactured and supplied by the firm. We gratefully acknowledge their support.

Accepted tor publication 23 February 1990.

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DANISH MEDICAL BULLETIN

VOL. 37 NO. 3 JUNE 1990 PAGES 197-287