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Zinc Gluconate in the Treatment of Dysgeusia—a Randomized Clinical Trial

ABSTRACT

In the treatment of dysgeusia, the use of zinc has been frequently tried, with equivocal results. The aim of the present randomized clinical trial, which involved a sufficiently large sample, was therefore to determine the efficacy of zinc treatment. Fifty patients with idiopathic dysgeusia were carefully selected. Zinc gluconate (140 mg/day; n = 26) or placebo (lactose; n = 24) was randomly assigned to the patients. The patients on zinc improved in terms of gustatory function ($p < 0.001$) and rated the dysgeusia as being less severe ($p < 0.05$). Similarly, signs of depression in the zinc group were less severe (Beck Depression Inventory, $p < 0.05$; mood scale, $p < 0.05$). With the exception of the salivary calcium level, which was higher in the zinc patients ($p < 0.05$), no other significant group differences were found. In conclusion, zinc appears to improve general gustatory function and, consequently, general mood scores in dysgeusia patients.

KEY WORDS: dysgeusia, gustatory function, mood, zinc therapy.

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INTRODUCTION

The sense of taste is generally considered less important than vision and hearing. However, taste disorders can diminish the quality of life, lead to work-related problems, and, in rare instances, may even become a life-threatening hazard (Schiffman, 1983; Henkin, 1994; Ackerman and Kasbekar, 1997; Heckmann *et al.*, 2003). Dysgeusia is defined as a distorted gustatory perception or persistent gustatory sensation in the absence of gustatory stimulants (Deems *et al.*, 1991; Brand, 2000). Frequently, patients report a changed perception of gustatory stimuli. These stimuli are often perceived as bitter, sour, or metallic. Treatment with zinc has been attempted, but the results of clinical studies are equivocal (Schechter *et al.*, 1972; Henkin *et al.*, 1976, 1999; Stoll and Oepen, 1994; Heyneman, 1996; Seiden, 1997; Sakai *et al.*, 2002). Among the reasons for these discrepancies in the literature may be the small sample size, and the fact that the study designs include different causes of dysgeusia. The purpose of this study was to re-investigate the efficacy of zinc treatment in idiopathic dysgeusic patients, in a randomized, placebo-controlled design.

MATERIALS & METHODS

Patients

The dysgeusic patients who took part in this study were recruited from the specialized interdisciplinary consultation unit for the care of patients with orofacial diseases. The diagnosis of dysgeusia was based on the patients' reports (Deems *et al.*, 1991). From 1999 to 2001, 116 patients suffering mainly from a dysgeusic taste disorder were seen; 50 patients suffering from idiopathic dysgeusia were then enrolled in the study. The remaining 66 patients were excluded. These patients either had symptomatic dysgeusia due to allergies to a dental material, dysgeusia in combination with burning mouth syndrome (Heckmann *et al.*, 2001), systemic disease, neurological or psychiatric disease, or metabolic disease, or the dysgeusia was, in all probability, caused by drugs known to interfere with taste (Schiffman, 1983; Henkin, 1994; Ackerman and Kasbekar, 1997). Approval was obtained from the ethics committee of the University of Erlangen-Nuremberg (Nr. 2266), and the patients gave their written informed consent.

Blinding and Randomization

Before patient recruitment, blinding and randomization were performed by an independent individual using a special computer software program (RANDOM by Joern Loetsch, Institute of Clinical Pharmacology, University of Frankfurt, Germany). To this end, enrollment numbers were established, and the subjects to be investigated were randomized by being grouped. Each group was made up of four patients, *i.e.*, two were assigned zinc, and two were assigned placebo.

Screw-top bottles were prepared containing either 100 zinc gluconate tablets (140 mg, "Zink Verla"®) or 100 placebo tablets (lactose, "Placebo Lichtenstein 10

mm"). The bottles were sealed and labeled with the study code and the enrollment number. After the initial investigation for the baseline data, each patient was given an enrollment number and the corresponding screw-top bottle. The zinc and placebo showed no significant difference in taste. Neither patient nor investigator had any knowledge during the study as to whether the patient was being treated with zinc or placebo. When the study was complete, this information was then revealed by the independent individual.

Treatment

Zinc gluconate (140 mg/day, equivalent to 20 mg/day of elemental zinc; *cf.* Henkin *et al.*, 1999) and placebo were given to the patients, with 26 subjects receiving zinc (five men, 21 women; mean age, 61.1 yrs; age range, 41-82 yrs) and 24 subjects receiving placebo (two men, 22 women; mean age, 61.0 yrs; age range, 47-78 yrs). Patients were advised to swallow the drug whole on an empty stomach with ample water. The therapy lasted for 3 mos.

Primary and Secondary Endpoints

The two primary endpoints were the scores of the taste test and self-rated dysgeusia. Gustatory sensitivity was assessed by means of the taste test. To this end, filter paper strips impregnated with 4 different concentrations of 4 taste qualities were placed on the left and right sides of the anterior third of the patient's tongue, resulting in a total number of 32 paper strips (Müller *et al.*, 2003).

Before each administration of a taste strip, the patient's mouth was rinsed with water. The taste strips were presented in increasing concentrations. Taste qualities were applied in a randomized fashion at each of the 4 levels of concentration. With the tongue still extended, the subject was asked to identify the taste from a list with the 4 descriptors—*i.e.*, sweet, sour, salty, bitter—and the respective 4 concentrations (sweet = 0.4, 0.2, 0.1, 0.05 g/mL sucrose; sour = 0.3, 0.165, 0.09, 0.05 g/mL citric acid; salty = 0.25, 0.1, 0.04, 0.016 g/mL NaCl; bitter = 0.006, 0.0024, 0.0009, 0.0004 g/mL quinine-hydrochloride). The correlation coefficient for test and re-test in healthy subjects was 0.68 (Müller *et al.*, 2003).

The self-rated impairment due to dysgeusia was recorded by means of a visual analogue scale (10-cm length is equivalent to 100%; no impairment = 0 units; extremely impaired = 10 units).

Secondary endpoints were the results of psychological tests related to depression (Beck Depression Inventory, BDI; Beck *et al.*, 1961) and mood (von Zersen mood scale, ZMS; Heimann *et al.*, 1975). In addition, the levels of zinc, sodium, calcium, potassium, and chloride in both the serum and saliva were analyzed. All measurements were taken before and after therapy.

Based on our clinical experience (Müller *et al.*, 2003), an improvement by 6 points in the taste test can be regarded as substantial, which typically also corresponds to the subjective feeling of an improved sense of taste.

Statistical Analysis

The results were evaluated with the use of SPSS 11 for Windows™. For the primary endpoints, an analysis of variance for repeated measurements was performed with the two within-subject factors 'session' (before, after therapy) and 'test' (taste test, self-rated dysgeusia), and the between-subject factor 'treatment' (zinc, placebo). Group comparisons were also performed with *t* tests for independent samples. For reasons of normalization, differences between the data obtained before and those obtained after therapy were computed. In addition, correlations (Pearson) were calculated between the variables of interest. The alpha level was set at 0.05.

RESULTS

All participants completed the study. The patients' characteristics are listed in the Table.

The characteristics of the two groups before treatment did not differ significantly. BDI and ZMS indicated a certain degree of depression and mood impairment according to published normative data (Beck *et al.*, 1961). During the observation period, none of the patients reported any treatment-associated side-effects. With regard to the primary endpoints,

Table. Characteristics of Patients Before and After Treatment (means, standard deviations [SD]; zinc group, n = 26; placebo group, n = 24) and Comparison of Data as Obtained before Treatment*

	Zinc Treatment (n = 24)				Placebo (n = 26)				Comparison of Data	
	Before		After		Before		After		Before Treatment	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	t-value	p-value
Age [yrs]	61.1	10.6			61.0	8.9			0.03	0.98
Duration of disease [mos]	39.8	41.3			47.6	68.6			0.54	0.59
Taste test [no. correctly identified out of 32]	17.1	5.8	25.7	6.5	18.9	7.3	21.2	5.7	1.12	0.27
Self-rated impairment [%]	40.7	5.9	45.0	4.4	42.6	5.7	43.8	3.6	1.23	0.23
Scores of Beck Depression Inventory (BDI)	10.6	8.5	7.5	7.0	11.3	10.7	11.3	10.9	0.28	0.78
Scores of Mood Scale (ZMS)	15.6	11.3	10.7	7.5	18.8	13.3	18.8	14.6	0.91	0.37
Zinc in serum [mg/dL]	72.78	18.38	81.53	19.61	67.90	14.64	72.01	10.22	1.01	0.32
Zinc in saliva [mg/dL]	5.95	3.65	9.04	13.04	4.51	3.53	6.22	4.46	1.42	0.16
Sodium in serum [mmol/L]	139.73	2.84	138.73	3.16	140.17	1.76	138.88	2.88	0.65	0.52
Sodium in saliva [mmol/L]	9.82	4.11	11.00	5.78	9.43	4.95	9.46	2.77	0.30	0.77
Potassium in serum [mmol/L]	4.14	0.58	4.32	0.42	4.40	0.46	4.65	1.25	1.76	0.09
Potassium in saliva [mmol/L]	29.44	41.11	21.22	4.69	20.00	6.59	20.40	6.10	1.11	0.27
Calcium in serum [mmol/L]	2.40	0.09	2.40	0.09	2.39	0.07	2.39	0.16	0.82	0.42
Calcium in saliva [mmol/L]	1.19	0.36	1.38	0.59	1.28	0.53	1.17	0.44	0.76	0.45

* There was no significant difference between the data before and the data after treatment.

an analysis of variance indicated a significant difference between measurements obtained before and those obtained after therapy (factor 'session': $F = 52.6$, $p < 0.001$). In addition, the significant interaction between the factors 'session' and 'treatment' ($F = 17.1$, $p < 0.001$) indicated that treatment had differential effects on patients treated with placebo or with zinc. Specifically, the gustatory function of patients on zinc improved in comparison with that of controls ($t = 4.25$, $p < 0.001$), and the patients rated the dysgeusia as being less severe ($t = 2.04$, $p = 0.048$) (Fig.).

In terms of patient ratings of improvement in dysgeusia (defined as an improvement of more than 5%), actual improvement was seen in 13 of 26 patients receiving zinc treatment (50%), while in the case of those receiving placebo (25%), improvement was found in only six of the 24 patients. In addition, zinc patients indicating improvement in dysgeusia also exhibited an average improvement (by 10.7 points) in their gustatory test scores, while the corresponding placebo patients exhibited an average improvement of only 2.7 points. In patients who had not indicated any improvement in dysgeusia, average taste scores were found to increase by 6.4 points in zinc patients and by 2.2 points in placebo patients.

When the secondary endpoints were reviewed, signs of depression or lowered mood were found to have improved in the zinc group (BDI score, $t = 2.60$, $p = 0.012$; ZMS, $t = 2.13$, $p = 0.039$). No significant group differences were seen for the other parameters investigated, with the exception of the salivary calcium level, which was higher in zinc patients than in controls ($t = 2.18$, $p = 0.034$). Interestingly, treatment with zinc had no significant effect on levels of zinc measured in serum ($t = 0.83$, $p = 0.41$) or saliva ($t = 0.46$, $p = 0.65$).

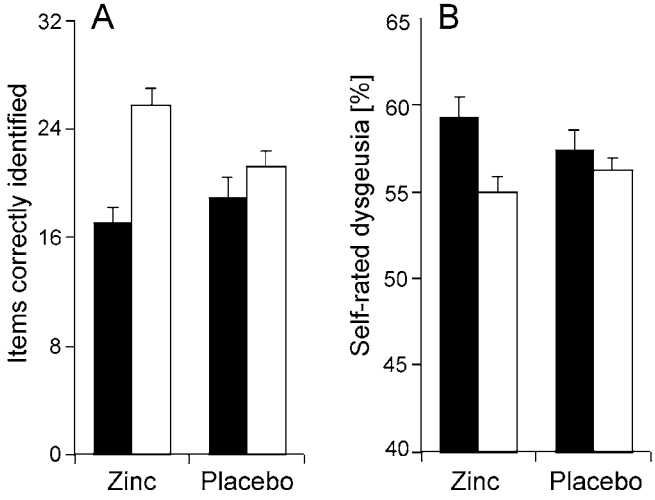

Figure. Taste test [number of taste strips (out of 32) correctly identified; **(A)** and self-rated dysgeusia (in % of the visual analogue scale; **(B)** before (black bars) and after (white bars) therapy (means, standard errors of means; zinc group, n = 26; placebo group. n = 24).

DISCUSSION

The results of this study indicate that zinc is useful in the treatment of dysgeusia in terms of improvement of general gustatory function. Dysgeusic sensations and general mood scores also improved. Unexpectedly, these findings appeared to be independent of the actual levels of zinc in serum or saliva.

Treatment with zinc in cases of dysgeusia is frequently recommended (Heyneman, 1996), although the results of published studies are equivocal. Reasons for these discrepancies are, among other things, the small sample size, the open trial design, inhomogeneous patient diagnosis involving patients with smell disorder or symptomatic dysgeusia, and the inclusion of zinc-deficient patients (Schechter *et al.*, 1972; Henkin *et al.*, 1976, 1999; Stoll and Oepen, 1994; Sakai *et al.*, 2002). To prevent bias and to ensure that the groups of patients studied were homogeneous, we enrolled only patients with idiopathic dysgeusia and, hence, a normal serum zinc level.

In the study at hand, there was a striking gender imbalance, with more females than males suffering from dysgeusia. This is consistent with the clinical experience of our unit for the care of patients with orofacial diseases (Heckmann *et al.*, 2001). It has been suggested that, among other things, hormonal changes may be responsible for the initiation of this symptom (Levenson, 2002).

No significant increase in serum zinc was found in the zinc group. This may be due to the fact that zinc is a trace element and is rapidly transferred into the cells. Zinc is of particular significance, especially in cells with a high-rate turnover, such as cells of the taste buds (Henkin, 1994; Umeta *et al.*, 2000). Thus, for the zinc dosage used, the insignificant change in serum zinc can be explained.

No side-effects were reported in the present study. At higher dosages, however, several side-effects can occur, such as gastrointestinal or hematological disorders—*e.g.,* anemia, leukopenia, and neutropenia (Salzman *et al.*, 2002)—and zinc intoxication can occur in cases of extreme dosage (Chobanian, 1981).

The presence of elevated salivary calcium in the zinc-treated patients is difficult to interpret. Our speculations center on an increased calcium secretion due to the influence of zinc. In previous studies, a salivary calcium-zinc exchange was observed, whereby the absorption of zinc led to a release of calcium (Ingram *et al.*, 1992).

Several basic scientific studies indicate that zinc is an extremely important factor in gustation. For example, zinc appears to be of significance for the regeneration of taste bud cells (Henkin *et al.*, 1999). Zinc also seems to be crucial in the regulation of metalloprotein expression and, in turn, for the synthesis of growth hormones. Finally, zinc is assumed to influence the activity of carbonic anhydrase VI, and thus, the level of gustin, an important metalloprotein which has been reported to act as a growth factor for taste bud cells (Henkin *et al.*, 1988). However, since the exact role that zinc plays in gustation is not fully understood, further research is necessary to explore the molecular and biological mechanisms underlying the effects of zinc on taste (Seiden, 1997). Nevertheless, from an empirical point of view, analysis of the current data suggests that treatment with zinc is helpful in treating patients with idiopathic dysgeusia.

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ERRATUM

In the manuscript, "Zinc Gluconate in the Treatment of Dysgeusia—a Randomized Clinical Trial" (*J Dent Res* 84:35-38), two of the entries in the Table on page 36 are incorrect. The corrected text appears in bold below. The authors regret the error.

Table. Characteristics of Patients Before and After Treatment (means, standard deviations [SD]; zinc group, n = 26; placebo group, n = 24) and Comparison of Data as Obtained before Treatment*

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Scores of Mood Scale (ZMS)	15.6	11.3	10.7	7.5	18.8	13.3	18.8	14.6	0.91	0.37
Zinc in serum **[microgram/dL]**	72.78	18.38	81.53	19.61	67.90	14.64	72.01	10.22	1.01	0.32
Zinc in saliva **[microgram/dL]**	5.95	3.65	9.04	13.04	4.51	3.53	6.22	4.46	1.42	0.16
Sodium in serum [mmol/L]	139.73	2.84	138.73	3.16	140.17	1.76	138.88	2.88	0.65	0.52
Sodium in saliva [mmol/L]	9.82	4.11	11.00	5.78	9.43	4.95	9.46	2.77	0.30	0.77
Potassium in serum [mmol/L]	4.14	0.58	4.32	0.42	4.40	0.46	4.65	1.25	1.76	0.09
Potassium in saliva [mmol/L]	29.44	41.11	21.22	4.69	20.00	6.59	20.40	6.10	1.11	0.27
Calcium in serum [mmol/L]	2.40	0.09	2.40	0.09	2.39	0.07	2.39	0.16	0.82	0.42
Calcium in saliva [mmol/L]	1.19	0.36	1.38	0.59	1.28	0.53	1.17	0.44	0.76	0.45

* There was no significant difference between the data before and the data after treatment.