A Bioavailability Study Comparing Two Oral Formulations Containing Zinc (Zn Bis-Glycinate vs. Zn Gluconate) After a Single Administration to Twelve Healthy Female Volunteers

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Abstract: As the current nutritional zinc intake frequently falls outside the Dietary Reference Intake (DRI) and as zinc is an essential trace mineral involved in the function of many enzymes, zinc supplementation has been recommended to prevent or treat the adverse effects of zinc deficiency. The aim of the present study was to compare the oral bioavailability of zinc bis-glycinate (a new formulation) with zinc gluconate (reference formulation). A randomized, cross-over study was conducted in 12 female volunteers. The two products were administrated orally at the single dose of 15 mg (7.5 mg × 2), with a 7-day wash-out period between the two tests. Serum concentrations of zinc were assayed by a validated inductively coupled plasma optical emission spectrometry (ICP-OES) method and C_{max}, T_{max}, and areas-under-the-curve (AUCs) were determined. The comparison between the two treatments was performed by comparing the C_{max}, AUC_t, and AUC_{inf} using an analysis of variance followed by the calculation of the 90% confidence intervals of the ratio test/reference.

Bis-glycinate administration was safe and well tolerated and bis-glycinate significantly increased the oral bioavailability of zinc (+43.4%) compared with the gluconate.

Key words: Zinc, bis-glycinate, gluconate, oral bioavailability, Dietary Reference Intake

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Introduction

Today, low zinc intake is of concern because this essential trace mineral is involved in the functioning of over 100 enzymes, ranging from DNA and RNA polymerases to catalase and alcohol dehydrogenase [1]. Unfortunately, present nutritional zinc intake frequently falls outside the U.S. and European Dietary Reference Intake (DRI). The DRI is a set of guidelines established in 1977 to give more detailed guidance than the Recommended Dietary Allowance (RDA) system that preceded it. The DRI is composed of the Estimated Average Requirement (EAR), expected to satisfy the needs of 50% of the people in that age group, the RDA, the Adequate Intake (AI) where no RDA has been established, and the tolerable Upper intake Levels (UL) to caution against excessive intake of nutrients that can be harmful in large amounts. In the case of zinc, the DRI is composed of a RDA/AI of 15 mg/day and an UL of 40 mg/day for an adult male [2–4].

Zinc supplementation has been recommended to prevent or treat the adverse effects of zinc deficiency on health, which frequently occurs in some physiological and pathological states [5–10]. In addition, the administration of pharmacological doses of the element has been used as a treatment for several disorders, such as inflammatory acne [11], immune disturbances [12], peptic ulcer [13], the common cold [14], or in Wilson's disease [15, 16].

Various zinc complexes (zinc picolinate, citrate, and gluconate) [17–19] tested at doses below or around the DRI [4] have the particularity of enhancing the oral bioavailability of zinc compared with zinc sulfate naturally present in food. Zinc bis-glycinate is a new chelate formed by two glycine molecules bound to a zinc cation, resulting in a double heterocyclic ring compound. The carboxyl group of each glycine is linked to the zinc by an ionic bond, whereas the α-amino group is joined to the metal by a coordinate covalent bond [20]. Given the data obtained with iron bis-glycinate, zinc bis-glycinate should increase the oral bioavailability of zinc. Indeed, iron bis-glycinate is more effective in the treatment of iron deficiency than supplementation with other products, notably the commonly used ferrous sulfate [21] which is correlated with a higher iron bioavailability [22, 23]. The question to be answered was if similar results could be obtained with zinc bis-glycinate.

The aim of our study was to compare the absorption of zinc by twelve healthy female volunteers after a single oral administration of zinc bis-glycinate (new formulation) or zinc gluconate (reference formulation).

Subjects and Methods

Subjects

Twelve healthy female Caucasian volunteers, aged between 18 and 40 and with a body mass index (BMI) ranging from 18 to 28, were selected for the study. Subjects were excluded if they had acute or chronic disorders that might interfere with drug absorption, allergy to zinc, drug or alcohol abuse, abnormalities in standard laboratory tests, or a positive pregnancy test. Ethical committee approval (Hôtel Dieu, Place de l'Hôpital, 69288 Lyon cedex 02, France) was obtained on July 19, 2005, prior to the start of the study (28 July 2005) in accordance with legal requirements. All subjects gave written consent.

Study Protocol

This study was an open, randomized, two-way, cross-over, single-dose study. The clinical phase of the study was conducted at the clinical investigation center OPTIMED S.A. (Gières, France). Twelve healthy female volunteers received a single oral dose of 15 mg of zinc (7.5 mg × 2) as zinc gluconate (reference treatment: dragée) or zinc bis-glycinate (test treatment: tablet). The two treatments contained vitamins of group B (B1, B2, B3, B5, B6, and biotin), cysteine (55 mg/dragée), and zinc (7.5 mg/dose). The two administration periods were separated by a 7-day wash-out interval where no zinc (gluconate or bis-glycinate) was taken in order to prevent any carry-over effect.

Subjects were required to attend the clinical unit in the morning and remained resident under permanent medical and nursing supervision for 8 hours. Before the morning administration, the volunteers were fasted for approximately 10 hours. The study products (zinc gluconate and zinc bis-glycinate) were swallowed as 2 tablets, neither chewed nor crushed, with exactly 200 mL of bottled spring water (low mineral content).

Blood sampling was performed before administration (0) and at 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, and 8.0 hours after dosing. Blood samples were collected into dry tubes (without additives) and centrifuged (3000 rpm for 10 minutes at 4°C) immediately after collection. Each serum sample was collected into two dry tubes, frozen and stored at –20°C prior to batch analysis.

The evaluation of safety included monitoring of any clinical adverse events (AEs) as well as vital signs (blood pressure, heart rate, respiratory rate, and body temperature) and biological parameters (biochemical and hematological). At the same time, a physical examination was performed to check the general appearance of the skin, eyes, ears, nose, throat, the mouth, the lymph nodes, and the skeleton (spine and extremities).

Clinical observations and biological laboratory data collected from the first administration until the end of the study or subject discontinuation were compared with baseline data obtained at the examinations during the screening visit.

Analytical Methods

The analytical phase of the study was conducted in a blind manner at ADME Bioanalyses (Vergèze, France). Zinc was measured in the serum by an inductively coupled plasma optical emission spectrometer (ICP-OES) method previously validated according to Arlington criteria [24]. The repeatability (precision: 4.4%–11.2%; accuracy: 92.5%–104.4%) and the reproducibility (precision: 5.6%–10.9%; accuracy: 94.9%–102.9%) have been demonstrated at 750, 2500, and 4000 ng/mL.

In brief, 0.5 mL of human serum was centrifuged (5 minutes at about 3500 rpm) at 4°C in a polypropylene tube (10 mL). Fifty µL of deionized water were added to the supernatant to equalize the quality control and the calibration volumes. The sample was then diluted with deionized water, thoroughly mixed for 10 seconds, and centrifuged for 5 minutes at 3500 rpm at 4°C. The supernatant was kept in hermetically sealed vials before ICP analysis (260 nm). No internal standard was used for the assay of zinc. The calibration curve was linear from 250 ng/mL (lower limit of quantification) to 5000 ng/mL (upper limit of quantification).

Pharmacokinetic and Statistical Analysis

The interpretation of the drug time-concentration curves for each volunteer and for each treatment schedule (zinc bis-glycinate and zinc gluconate) was performed with the software Kinetica (Version 4.3 – Thermoelectron Corporation – Philadelphia, USA), using an independent-modelling calculation. The pharmacokinetic parameters for zinc were (1) AUC_t, the area under the serum concentration vs. time curve from 0 to the last measurable concentration (C_{last}), calculated using the trapezoidal method; (2) AUC_{inf}, the area under serum concentration vs. time curve from 0 to infinity, calculated as the sum of the AUC_t + C_{last}/k_e. k_e is the first-order terminal constant rate calculated from a semi-log plot of the serum concentration vs. time curve; (3) $t_{1/2}$, the terminal half-life calculated as $\ln(2)/k_e$; and (4) C_{max} and T_{max}, the maximum measured serum concentration and the time to reach it, respectively.

All the descriptive statistics were performed on the concentration data and pharmacokinetic parameters. Pharmacokinetic results were presented as the mean (± S.D.), and T_{max} median, minimum (min), and maximum (max) values are also presented.

The comparison between the two treatments (zinc bis-glycinate vs. zinc gluconate) was performed by comparing the C_{max}, AUC_t, and AUC_{inf}, using an analysis of variance followed by the calculation of the 90% confidence intervals of the ratio test/reference. Values of C_{max} and AUCs were a *priori* log-transformed. It was concluded that there was no difference if the corresponding 90% confidence intervals for the ratio of the means were between 0.80 and 1.25 [25]. For the statistical comparison of the T_{max}, the Friedman test was performed with $p < 0.05$ [25].

Results

Clinical responses to zinc (gluconate or bis-glycinate) administration

During the overall study period, 2 of 12 (16.7%) subjects reported the occurrence of adverse events: one of a moderate headache and one of a mild hot flush. These adverse events occurred after the administration of zinc gluconate and were considered to be "not related" to the study drug, and were resolved before the end of the study. One adverse event (headache) required a concomitant treatment (paracetamol, 1000 mg). No serious adverse events were seen during this study.

No relevant change in the vital signs (blood pressure, heart rate, respiratory rate, and body temperature), in the physical examination and in the biological (biochemical and hematological) parameters was observed between the initial screening and the examinations at the end of the study.

Pharmacokinetic parameters of zinc

The mean (± S.D.) serum concentration-time curves of zinc after a single oral administration of 7.5 mg × 2 zinc as zinc gluconate (reference treatment) and as zinc bis-glycinate (test treatment) in twelve female volunteers are presented in Figure 1. The corresponding pharmacokinetic parameters with the statistical interpretation are shown in Table I.

The mean C_{max}, AUC_t, and AUC_{inf} of zinc were significantly different between the two treatment schedules (Table I) with a ratio $C_{max(TEST)}/C_{max(REFERENCE)}$ of 1.41 and a 90% CI of 1.26–1.79, a ratio $AUC_{t(TEST)}/AUC_{t(REFERENCE)}$ of 1.42 and a 90% CI of 1.23–1.71, and a ratio $AUC_{inf(TEST)}/AUC_{inf(REFERENCE)}$ of 1.38 and a 90% CI of 1.22–1.58. All the 90% CIs were out of the reference range 0.8–1.25. Consequently, zinc bis-glycinate is not bioequivalent to zinc gluconate and gives a higher bioavailability. Indeed, the relative bioavailability of zinc bis-

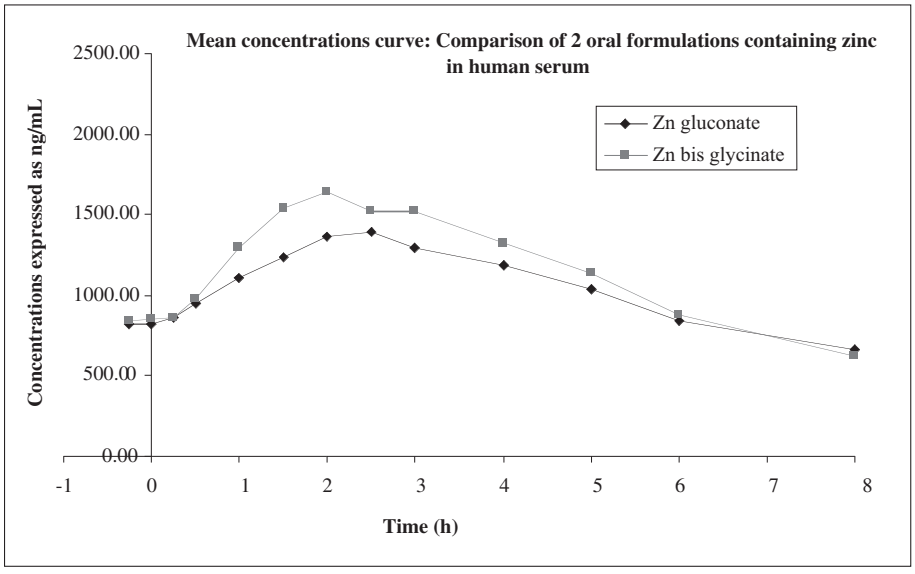

Figure 1: Mean of zinc serum concentrations vs. time measured after a single oral administration of 7.5 mg × 2 zinc as gluconate (reference treatment) and bis-glycinate (test treatment) in twelve healthy female volunteers.

Table I: Mean (± S.D.) pharmacokinetic parameters calculated after a single oral administration of 7.5 mg × 2 zinc as zinc gluconate (reference treatment) or zinc bis-glycinate (test treatment) in twelve healthy female volunteers and statistical interpretation (ANOVA and CI $_{90\%}$ of the ratio of the C_{max} and the AUCs and Friedman test for T_{max})

	PK Parameters	zinc gluconate (reference) mean ± SD	zinc bis-glycinate (test) mean ± SD	ANOVA test vs reference	Ratio (test/ reference) mean	confidence interval $CI_{90\%}$
zinc	C_{max} (ng/mL)	650.61± 256.74	919.49 ± 148.86	p = 0.002 (S)	1.41	1.26–1.79
	AUC_t (ng/mL × h)	1917.99 ± 577.20	2718.04 ± 615.47	p = 0.002 (S)	1.42	1.23–1.71
	AUC_{inf} (ng/mL × h)	2193.81± 514.11	3028.89 ± 561.65	p = 0.001 (S)	1.38	1.22–1.58
	PK Parameters	zinc gluconate (reference) mean ± SD	zinc bis-glycinate (test) mean ± SD	ANOVA test vs reference		
zinc	T_{max} (h)	2.25 ± 0.40	2.13 ± 0.53	L = 0.333 (NS)		
	median (min/max)	2.25 (1.5/3.0)	2.00 (1.5/3.0)			

S: significant
NS: not significant

glycinate treatment compared with zinc gluconate was 143.44% ± 25.78%.

The statistical interpretation of the T_{max} did not reveal any significant variation and the values were 2.25 and 2.13 hours for the reference and the test, respectively.

Discussion

Zinc bis-glycinate was safe and well tolerated when administered to the twelve healthy female volunteers as a single dose. Two subjects (2/12: 16.7%) reported minor adverse events after administration of zinc gluconate: one episode of headache and one episode of hot flush, respectively, and these were considered to be "not related" to the study drug. Concerning the vital signs, the physical examination, and the biological laboratory tests, there was no significant difference between the examinations at screening and during the test period for each of the two products.

The statistical interpretation of the pharmacokinetic results showed that the oral bioavailable fraction was significantly higher with zinc bis-glycinate than with zinc gluconate without any change in the absorption rate (no significant variation of the T_{max}). Indeed, all the pharmacokinetic ratios were beyond the range 0.8–1.25 and the increase in the oral bioavailability of zinc was 43.44%.

Our results (C_{max} and AUC) with zinc gluconate were slightly higher than those reported by other authors, taking into account the difference of dosage. For example, Neve *et al* [18,19] obtained a C_{max} of 1140 ng/mL, a T_{max}

of 2.3 hours (h) and an AUC_{inf} of 4670 ng/mL × h after a single oral dose of zinc (15 mg × 3) as zinc gluconate (Rubozinc®). This difference may be easily explained by a non-linearity of the pharmacokinetics of zinc for doses over 20 mg due to a saturation of the oral absorption, as was reported by Tran *et al* [26]. Moreover, the chemical form of zinc (salt or chelate), the pharmaceutical formulation (presence of excipients), and the division of the administered dose are other factors that modify the oral bioavailability of zinc [18]. Considering the pharmaceutical formulation, Neve *et al* [18] noted a decrease in the oral bioavailability of zinc when zinc gluconate was associated with starch, lactose, hydrated silica, and magnesium stearate (excipients present in Rubozinc®), compared with zinc gluconate without excipients.

In the case of our results, the significantly higher oral bioavailability of zinc when administered as bis-glycinate compared with gluconate is not surprising, given that bis-glycinate enhances the oral bioavailability of others ions, particularly iron. Kapsokefalou *et al* [23] compared the solubility and dialyzability of iron fortificants (iron pyrophosphate, ferrous bis-glycinate, ferrous gluconate, ferrous lactate, and ferrous sulfate) added to pasteurized milk samples produced under laboratory conditions. Ferrous dialyzable iron (molecular weight lower than 8000 daltons) was used as an index for the prediction of oral bioavailability. The authors observed that ferrous bis-glycinate exhibited higher dialyzability (5.7 ± 3.0%) than ferrous gluconate (4.2 ± 3.0%). Similarly, Olivares *et al* [22] reported a higher oral bioavailability of iron when administered as bis-glycinate (34.6%) than ascorbate (29.9%).

The higher absorption of zinc when chelated with bis-glycinate may well be explained by its chemical structure [27]. Firstly, each glycinate molecule contains two functional groups that are capable of entering into covalent and coordinate covalent bonds with zinc. Secondly, each one can create a ring structure with the zinc ion and form a sterically and energetically stable structure. Thirdly, zinc bis-glycinate has a low molecular weight (< 1000 daltons) and is able to cross cell membranes. Lastly, the bis-glycinate chelate is not affected by pH changes from 2 to 6 [28]. Consequently, bis-glycinate may protect a significant fraction of the zinc from interactions with lumenal gastro-intestinal components, dietary components, and drugs [29] whereas in the current salts, the zinc may not be protected from such interactions. Lopez de Romana *et al* [30] measured zinc absorption from wheat products fortified with either zinc sulfate or zinc oxide. Eleven adult volunteers received either low-phytate bread (n = 11) or higher-phytate porridge (n = 11) once weekly on two occasions. The food was fortified with 1 of the 2 zinc salts (60 mg elemental Zn/kg wheat flour) during week 1 and with the other during week 2, in random order. ^{65}Zn in the same chemical form as the fortificant was incorporated into each food to assess zinc absorption with the use of whole-body counting. The authors reported that Zn absorption from bread (13.8%; 95%CI: 11.8%–16.2%) was significantly ($p < 0.001$) greater than the porridge (6.4%; 5.5%–7.6%), presumably because of greater phytate content of porridge. With control for food type, there were no significant differences in zinc absorption from meals fortified with zinc sulfate or zinc oxide ($p = 0.24$).

Similarly, Ferdlund and *et al* [31] studied the dose-dependent inhibitory effect of sodium phytate (*myo*-inositol-hexaphosphate) on zinc absorption in man. Forty subjects were served meals containing white wheat rolls without/with additions of phytate. Ten subjects were given test meals containing one or two of the studied levels of phytate and in addition all subjects were served meals to which no phytate was added. The zinc (inorganic salt) content was 3.1 mg (47 μmol). The rolls were labelled extrinsically with radioisotopes (^{65}Zn) and whole-body retention was measured. The zinc absorption in meals to which either 0, 25, 50, 75, 100, 140, 175, or 250 mg of phytate-P (0, 134, 269, 403, 538, 753, 941, or 1344 μmol) had been added was 22%, 16%, 14%, 11%, 7%, 7%, 7%, and 6%, respectively (mean values). The addition of 50 mg phytate-P or more significantly decreased zinc absorption ($p = 0.01$) as compared to absorption from the test meals with no added phytate. It was concluded that the inhibitory effect of phytate on the absorption of zinc was dose-dependent.

In conclusion, our results clearly demonstrate that zinc bis-glycinate is safe and well-tolerated, and significantly increases the oral bioavailability of zinc (increase of 43.44%) compared with the gluconate salt. In the case where the nutritional zinc intake falls outside the RDI due to an interaction between zinc and phytates present in food, bis-glycinate of zinc may be an interesting supplement for achieving the physiologic requirement for zinc.

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