Different Effects of Polaprezinc and Zinc Chloride on Zinc Supplementation in Elderly Bedridden Patients Receiving Enteral Nutrition

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Aims : The purposes of this study were to compare the effects of polaprezinc and zinc chloride on serum zinc and copper concentrations in elderly bedridden patients receiving enteral nutrition, and to examine the effects of polaprezinc on pressure ulcer healing in those patients. Methods : Seven elderly bedridden patients receiving enteral nutrition entered into a crossover study of 2-week treatment periods with polaprezinc or zinc chloride, separated by a 4-week washout period. Serum zinc and copper concentrations were compared between both treatment periods. Then, another five elderly patients with pressure ulcers were treated with polaprezinc for 8 weeks. The assessment of pressure ulcers was made weekly using the PUSH tool 3.0. Results : After 2 weeks, polaprezinc significantly increased serum zinc concentrations, decreased serum copper/zinc ratios, but did not change serum copper concentrations. Zinc chloride did not change these three parameters. Polaprezinc also produced a significant improvement in PUSH score and a reduction of 81% in ulcer area after 8 weeks. Conclusion : The efficiency of absorption of zinc from polaprezinc may be much higher than that from zinc chloride in elderly bedridden patients receiving enteral nutrition. Polaprezinc may also have a beneficial effect on pressure ulcer healing in those patients. (Kitakanto Med J 2011 : 61 : 275~280)

Key words : polaprezinc, zinc supplementation, elderly, pressure ulcer, enteral nutrition

Introduction

Zinc, an essential trace element in the human body, is known to serve as the active center of approximately 300 enzymes.¹ Zinc deficiency causes various pathological conditions such as growth retardation, immunodeficiency, and neurological degeneration. Zinc deficiency is typically the result of inadequate dietary intake of zinc, the recommended dietary allowance for zinc has been presented for healthy individuals in the “Dietary Reference Intakes for Japanese, 2005” by the Japanese Ministry of Health, Labor, and Welfare.² However, we have recently reported that zinc deficiency is common in elderly bedridden patients receiving long-term enteral nutrition based on the recommended dietary allowance, and that zinc deficiency may be associated with increased susceptibility to infections in those patients.³ ⁴ On the basis of the findings, we have proposed that zinc preparations should be added to the standard enteral formulas to prevent infectious diseases in elderly bedridden patients. Ordinarily, zinc preparations used for zinc therapy are inorganic salts (e.g., zinc sulphate, zinc picolinate, or zinc chloride) and organic compounds (e.g., polaprezinc or zinc gluconate). Previous studies have revealed the different activities for zinc therapy between inorganic salts and organic compounds.⁵ ⁶

We carried out a randomized crossover study to
compare organic zinc compounds with inorganic zinc salts, looking at whether there was a difference in their effects on serum zinc and copper concentrations in elderly bedridden patients receiving long-term standard enteral nutrition. We used zinc chloride as an inorganic salt and polaprezinc as an organic compound. Polaprezinc [N-(3-aminopropionyl)-L-histidinato zinc], a chelating compound of zinc ion and L-carnosine, is commonly used in the treatment of gastric ulcers in Japan. In addition, we carried out a pilot study to examine the therapeutic effects of polaprezinc on pressure ulcer healing in elderly bedridden patients receiving long-term standard enteral nutrition because zinc is essential for the wound-healing process.

Methods

The study was approved by the institutional ethics committee of Ninosawa Hospital and performed in accordance with the Declaration of Helsinki. We obtained informed written consent from the patients or the relatives if the patients had dementia or communication difficulties before participation.

Study 1

Subjects and Study Design

Seven elderly bedridden patients (4 men and 3 women; mean ± SD age, 84.3 ± 5.5 years) receiving long-term standard enteral nutrition were enrolled in this study. All patients received standard enteral nutrition consisting of a high-protein fluid with enriched microelements (Meibaransu HP1.5; Meiji Dietaries Corporation, Tokyo, Japan). This formula provided nutrition containing 49.5g protein, 24.4g fat, 9.9 mg zinc, 0.5mg copper, 9.9mg iron with 1,000kcal per 660mL serving daily, fulfilling the “Dietary Reference Intakes for Japanese, 2005”

This study was a crossover study of zinc chloride and polaprezinc, which comprised a 2-week run-in period and two treatment periods of 2 weeks duration with a washout period of 4 weeks between two treatments. After the run-in period, the patients were randomized to receive zinc chloride or polaprezinc for 2 weeks. The drug doses were polaprezinc 150mg/day (containing 34mg of zinc) or zinc chloride 70mg/day (containing 34mg of zinc) during treatment period. After a 4-week washout, patients receiving zinc chloride switched to polaprezinc, and vice versa.

Polaprezinc was purchased from Zeria Pharmaceutical Co., Ltd., Tokyo, Japan. Zinc chloride was purchased from Koso Chemical Co., Ltd., Tokyo, Japan.

Blood Biochemistry

Blood samples were collected in the morning at the beginning (baseline) and the end (week 2) of each treatment period for serum zinc and copper concentrations. Serum zinc concentrations were evaluated using flame atomic absorption spectrometry. Serum copper concentrations were determined by colorimetric assay.

Study 2

Subjects and Study Design

Five elderly bedridden patients (3 men and 2 women; mean ± SD age, 78.4 ± 11.2 years) with pressure ulcers were enrolled in this study. Two patients had stage III ulcers, and three had stage IV ulcers according to the National Pressure Ulcer Advisory Panel staging system, 2007. All patients received standard enteral nutrition consisting of a high-protein fluid with enriched microelements (Meibaransu HP1.5; Meiji Dietaries Corporation, Tokyo, Japan). Patients were excluded if they had acute illness (e.g., infection) or chronic disease (e.g., diabetes mellitus, peripheral vascular disease, autoimmune or neoplastic disorders).

This study was designed to evaluate the therapeutic effects of polaprezinc on pressure ulcer healing in elderly bedridden patients receiving standard enteral nutrition. The patients were given polaprezinc 150 mg/day during a treatment periods of 8 weeks. Pressure ulcer care including patient repositioning schedules, bed and mattress type and dressings were kept constant during the 8-week treatment period and according to standard hospital practice.

Pressure Ulcer Measurements

The assessment of pressure ulcers were made weekly using the PUSH tool 3.0 (Pressure Ulcer Scale for Healing) throughout the 8-week treatment period. The PUSH tool was developed by the National Pressure Ulcer Advisory Panel as a quick and reliable tool to monitor the change in pressure ulcer status over time. The PUSH tool has a sub-score for (a) surface area (length x width), (b) exudate amount, and (c) tissue type. The sub-scores were then added together to give a PUSH total score on a scale of 0 (completely healed) to 17 (greatest severity). A comparison of total scores measured over time provided an indication of the improvement or deterioration in pressure ulcer healing.

Blood Biochemistry

Biochemical data were collected in the morning at
weeks 0 (baseline), 4, and 8 of the treatment period. Blood measurements included hemoglobin, lymphocyte counts, and serum concentrations of total protein, albumin, pre-albumin, transferrin, zinc, copper, total cholesterol, and C-reactive protein.

**Statistical Analysis**

Data are presented as mean±SD. Comparisons of between-treatment and within-treatment quantitative variables were performed using paired Student t-test. Changes in PUSH score, pressure ulcer area, and biochemical parameters from baseline to 8-week follow-up were analyzed using analysis of variance (ANOVA) for repeated measures followed by the Dunnett post hoc tests. A P value of <0.05 was regarded as significant. All statistical analyses were performed with SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

**Results**

**Study 1**

The underlying diseases of the 7 elderly bedridden patients included disuse syndrome for 5 patients (72%), cerebral infarction for one (14%), and subarachnoid hemorrhage for one (14%). The mean baseline biochemical data were hemoglobin, 12.5±2.5 g/dL; total protein, 6.2±0.4 g/dL; albumin, 3.3±0.3 g/dL; total cholesterol, 154±41 mg/dL; and C-reactive protein, 1.1±1.2 mg/dL.

Figure 1 shows the changes in serum concentrations of zinc and copper, and serum copper/zinc ratio during the 2-week treatment period with polaprezinc (closed circle, n=7) or zinc chloride (open circle, n=7). There were no statistically significant differences between both treatments for any of serum concentrations of zinc and copper, and serum copper/zinc ratios at baseline. Serum zinc concentrations at baseline were below the lower limit of the normal range (65-110μg/dL). Serum zinc concentrations significantly increased from 53.7±8.7 to 69.6±14.3μg/dL during the treatment period with polaprezinc (P<0.05), but they did not change during the treatment period with zinc chloride. The percentage increase in serum zinc concentrations during the treatment period with polaprezinc was 30%, which was greater than during the treatment period with zinc chloride (15%) but not statistically significant. An increase of >5% occurred in 7/7 patients (100%) during the treatment period with polaprezinc but in only 4/7 (57%) during the treatment period with zinc chloride (P=0.0507, Fisher’s exact test). Serum copper concentrations did not change during both treatment periods. We also calculated serum copper/zinc ratio because copper and zinc interact during intestinal absorption. Serum copper/zinc ratios significantly decreased from 1.75±0.39 to 1.28±0.34 during the treatment period with polaprezinc (P<0.05), but they did not change during the treatment period with zinc chloride.

**Study 2**

Figure 2 shows the changes in pressure ulcer
Fig. 2 Changes in pressure ulcer severity as measured by the PUSH score and ulcer area during the 8-week treatment period with polaprezinc. Data are presented as mean±SD. *P<0.05 vs. baseline.

Table 1 Changes in biochemical parameters during the 8-week treatment period with polaprezinc

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.5±1.4</td>
<td>10.3±1.7</td>
<td>10.2±1.6</td>
</tr>
<tr>
<td>Lymphocyte (/mm³)</td>
<td>1.79±0.670</td>
<td>2.23±0.870</td>
<td>1.89±0.750</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.0±0.5</td>
<td>3.0±0.5</td>
<td>3.1±0.5</td>
</tr>
<tr>
<td>Pre-albumin (g/dL)</td>
<td>17.4±3.3</td>
<td>18.0±4.3</td>
<td>21.4±7.5</td>
</tr>
<tr>
<td>Transferrin (mg/dL)</td>
<td>193.8±43.5</td>
<td>189.8±44.4</td>
<td>193.2±44.4</td>
</tr>
<tr>
<td>Zinc (μg/dL)</td>
<td>47.4±7.0</td>
<td>78.4±12.0*</td>
<td>92.2±9.9**</td>
</tr>
<tr>
<td>Copper (μg/dL)</td>
<td>141.2±14.0</td>
<td>124.0±19.5*</td>
<td>96.0±27.1*</td>
</tr>
<tr>
<td>Cu/Zn ratio</td>
<td>3.1±0.7</td>
<td>1.6±0.4*</td>
<td>1.1±0.3**</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>161±21</td>
<td>165±15</td>
<td>170±22</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>2.6±2.7</td>
<td>2.3±1.8</td>
<td>2.1±1.1</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. *P<0.01 vs. baseline. **P<0.001 vs. baseline.

severity as measured by the PUSH score and ulcer area during the 8-week treatment period with polaprezinc. There was a significant improvement in PUSH score from 11.8±2.6 at baseline to 6.4±4.4 at week 8 (P<0.05). Ulcer area also significantly reduced from 10.3±11.2cm² at baseline to 2.0±2.3cm² at week 8, which is a reduction of 81% (P<0.05). An example of complete wound closure of stage IV ulcer is depicted.
in Figure 3.

Table 1 shows the changes in biochemical parameters during the 8-week treatment period with polaprezinc. Serum zinc concentrations significantly increased from 47.4±7.0 μg/dL at baseline to 78.4±12.0 μg/dL at week 4 (P<0.01) and 92.2±9.9 μg/dL at week 8 (P<0.001). Serum copper concentrations significantly decreased from 141.2±14.0 μg/dL at baseline to 96.0±27.1 μg/dL at week 8 (P<0.01). Serum copper/zinc ratios significantly decreased from 3.1±0.7 at baseline to 1.6±0.4 at week 4 (P<0.01) and 1.1±0.3 at week 8 (P<0.001). There were no significant changes in hemoglobin, lymphocyte count, and serum concentrations of total protein, albumin, prealbumin, transferring, total cholesterol, and C-reactive protein.

Discussion

Effects of Polaprezinc on Serum Zinc Concentrations

This study demonstrated that serum zinc concentrations significantly increased during the 2-week treatment with polaprezinc but they did not change during the treatment with zinc chloride. The percentage increase in serum zinc concentrations tended to be greater during the treatment with polaprezinc than during the treatment with zinc chloride. These findings suggest that the efficiency of absorption of zinc from an organic zinc compound, polaprezinc may be much higher than that from an inorganic zinc salt, zinc chloride. Zinc is mainly absorbed in the small intestine, especially the duodenum and proximal jejunum.10,11 Zinc first binds to the apical membrane of the small intestinal cell, is transported into the cell, and then secreted into the blood.12 Two mechanisms are proposed to account for zinc absorption in the small intestine.1 One mechanism is an active transport process that zinc is absorbed from the small intestinal mucosa as organic compounds, composed of zinc and carriers such as citric acid, picric acid, amino acids such as histidine and cysteine, and a low-molecular weight metal-binding protein, metallothionein. The other mechanism is a passive transport process that zinc ion itself is absorbed from the brush border of the small intestinal mucosa. We speculate that the different effects of polaprezinc and zinc chloride on serum zinc concentrations may be related to the mechanisms responsible for zinc absorption. Polaprezinc comprises zinc and L-carnosine as mentioned above. It has been known that L-carnosine exerts a remarkable enhancing effect on zinc uptake.13

Effects of Polaprezinc on Serum Copper Concentrations

In this study, serum copper concentrations did not during the short-term (2-week) treatment periods with any of polaprezinc and zinc chloride. During the long-term (8-week) treatment with polaprezinc, serum copper concentrations significantly decreased but were within the normal range (68-128 μg/dL). It has been well known that copper and zinc interact during intestinal absorption, resulting in a decreased uptake of copper.14,15 The competitive interaction of copper and zinc is mediated by intracellular metallothioneines at the brush border of the small intestine.16,17 In the presence of zinc deficiency, absorption of copper is enhanced.18,19 As a result, a reduced serum zinc concentration, and an elevated serum copper concentration (over 120 μg/dL), and elevated serum copper/zinc ratio (1.5 or higher) are noted in the presence of zinc deficiency.19 Thus, serum copper concentrations and serum copper/zinc ratios can be used as reference information for diagnosing zinc deficiency. In this study, serum copper/zinc ratios were over 1.5 at baseline, but they were normalized during the treatment period with polaprezinc.

Effects of Polaprezinc on Pressure Ulcer Healing

Pressure ulcers are common in frail or bedridden elderly people and are associated with increased mortality and decreased quality of life.20–22 Malnutrition, inadequate protein or poor energy intake and recent weight loss have been identified as independent risk factors for the development of pressure ulcers.23–25 Wound healing is a complex process involving three stages of inflammation, proliferation, and maturation that occur on a continuum from injury to healing.26 On a cellular level, zinc is necessary for deoxyribonucleic acid (DNA) synthesis and replication, and therefore is essential for growth.27 Zinc plays a central role in the proliferation of inflammatory cells and modulates cutaneous inflammation.28 Throughout the proliferation and maturation phases, zinc is required for collagen synthesis. Zinc is also necessary for the proliferation of fibroblasts and keratinocytes and quickens the process of re-epithelialisation, while strengthening the wound.27,29 Thus, zinc has been shown to play a significant part in the wound-healing process, but the evidence regarding zinc supplementation is generally inconclusive. Our pilot study demonstrated that the 8-week treatment with an organic zinc compound, polaprezinc significantly improved the PUSH score and ulcer area in elderly bedridden patients receiving long-term standard enteral nutrition, and suggested that polaprezinc had a beneficial effect on pressure ulcer healing. These
results need to be confirmed in a randomized controlled trial.

In conclusion, the efficiency of absorption of zinc from polaprezinc may be much higher than that from zinc chloride in elderly bedridden patients receiving long-term standard enteral nutrition. Polaprezinc may also have a beneficial effect on pressure ulcer healing in those patients.

References

9. NPUAP (National Pressure Ulcer Advisory Panel) PUSH (Pressure Ulcer Scale for Healing) Tool Version 3.0. http://www.npuaap.org/push-3-0.htm