Research Article

Evaluation and comparison of zinc absorption level from 2-Alkyle 3-Hydroxy pyranon-zinc complexes and zinc sulfate in rat *in vivo*

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Abstract

Background: Although zinc sulfate has been used to improve disorders originated from zinc deficiency, its low compliance is due to gastrointestinal complications; therefore, other zinc compounds have been suggested as replacers for zinc deficient people. The objective of this study was to evaluate and compare the absorption of ethyl and methyl zinc-maltol with that of zinc sulfate to substitute zinc sulfate with those complexes.

Materials and Methods: After five weeks of being fed by zinc deficient food, zinc deficient rats were divided into four groups randomly receiving medicinal solutions of zinc sulfate, zinc ethyl maltol and zinc methyl maltol using feeding tube method for two weeks while the control was received distilled water. Serum zinc concentration and ALP (Alkaline Phosphatase) and LDH (Lactate Dehydrogenase) activity of rats were determined before and after the study. Statistical analyses were performed using SPSS 11.5. The study was conducted from 2008 to 2010.

Results: Serum zinc concentration and enzyme activity in all groups receiving drug solution increased. The most and least increase were in zinc sulfate and zinc methyl maltol groups, respectively. The difference between zinc methyl maltol and zinc sulfate group was significant ($P < 0.05$); however, this difference was not significant in the case of zinc ethyl maltol.

Conclusion: Zinc ethyl maltol can be a suitable and preferable substitute for zinc sulfate.

Key Words: Alkaline phosphatase, Lactate dehydrogenase, zinc ethyl maltol, zinc intestinal absorption, zinc methyl maltol, zinc sulfate

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INTRODUCTION

Zinc is an essential component of more than 300 enzymes which have a diverse range of functions.[1] ALP (Alkaline Phosphatase) and LDH (Lactate Dehydrogenase) are two enzymes whose activities depend on body zinc concentration. Zinc deficiency affects these enzymes activity negatively.[2,3] Zinc stabilizes the molecular structure of cellular compounds and membranes. Also,

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zinc has an essential role in transcription and thus genetic expression.[4] It plays a key role in immune system.[5] Its involvement in such fundamental activities accounts for the essentiality of zinc for all life form.

The clinical features of zinc deficiency in human are growth retardation,[6] delayed sexual maturation,[1] increased susceptibility to infections,[7,8] impairment of immune defense,[9] and appearance of behavioral changes.[10]

An effective strategy to treat zinc deficiency is zinc supplementation. To reduce zinc deficiency and treat the resulting disorders, zinc compounds have been used for many years. The only medicinal product as a zinc dietary supplement in the market of Iran is zinc sulfate, which is produced either in bulk or capsule form. Not only the bioavailability but also the compliance of the product is low, because of gastrointestinal complications and drug interactions.[11]

Attempts have been made to solve the mentioned problems of zinc sulfate so far but more studies seem to be needed. One of the solutions in this respect is prescribing other zinc derivatives.

Ethyl and methyl maltol are used as non-toxic and edible compounds to enhance the taste and flavor of different foods. They have high reactivity with metals such as iron and zinc.[12] In contrast to ionic drugs, non-ionic drugs such as hydroxy pyranons penetrate and absorb more through intestine epithelial cells.[13,14] Since ethyl and methyl maltol are among 3-Hydroxy Pyran 4-ens, they are easily absorbable through intestine.[12] Complex of elemental zinc with methyl maltol (2-methyl 3-hydroxyl pyran 4-en) and ethyl maltol (ethyl 3-hydroxy pyran 4-en) is an effective compound for increasing zinc intestinal absorption and obtaining a non toxic and edible product without mentioned disadvantages of zinc sulfate.

The objective of this study was to synthesize zinc ethyl and methyl maltol complexes and then to evaluate and compare serum zinc concentration from these complexes with that of zinc sulfate. In this way it would be possible to achieve an effective drug to replace zinc sulfate with the least side effects for preventing and treating zinc deficiency.

MATERIALS AND METHODS

Study rats

This study was conducted from 2008 to 2010 in Isfahan University of Medical Science. Fifty male rats of Wistar breed were selected for this study. Rats were from Tehran Pastor Institute and were kept in the animal house of faculty of pharmacy in Isfahan University of Medical Science. To prevent the rats from infection, their cages had been disinfected with five in 1000 phenol solution.

Food preparation

In order to determine the actual effect of zinc complexes and zinc sulfate on serum zinc concentration, the rats had to become zinc deficient; therefore, they fed on dietary regime without zinc. Not only the diet was zinc deficient but also its soy content could inhibit zinc absorption and increase zinc secretion.[15,16] The following ingredients were included in the diet: Corn starch 312 g, sugar 360 g, egg albumin powder 200 g, soy 60 g, cellulose 60 g, multi vitamin-mineral 96 g, and corn oil 100 g.

Drug preparation

Methyl and ethyl maltol were purchased from Aldrich Company, England, and zinc sulfate from Alhavi Company, Iran. Complexes of zinc with ethyl and methyl maltol were synthesized and examined in faculty of pharmacy.[17] Drug solutions were prepared in a way that each contained 2.5 g zinc/Kg weight of rat.

Feeding rats, sample preparation and biochemical analyses

The rats were fed on zinc deficient food for five weeks. To make sure that all treated rats had become zinc deficient, serum zinc concentration and enzymes (ALP and LDH) activity of rats were measured. Serum zinc level was determined using Atomic Absorption Spectrophotometry (Perkin Elmer 2380) and ALP and LDH activity were measured by Pars Azmoon kit and Spectrophotometer (UV mini 1240), and Zist Shimi kit and Spectrophotometer, respectively. Afterwards, deficient rats were divided into three groups randomly receiving medicinal solutions of zinc sulfate, zinc ethyl maltol and zinc methyl maltol using feeding tube method for two weeks while control received distilled water in the same way. The number of rats in each group was 12. Rats were fed on 1µl of each solution per 1 g weight of rat. At the end of the study, serum biochemical markers (serum zinc level and enzymes activity) of all groups were measured.

Data management and statistical analyses

Statistical analyses were performed using SPSS 11.5. Data were presented as Means ± SD. Differences among the study groups for serum zinc concentration and enzymes activity were determined by ANOVA and Tukeys' Post Hoc Test. Results were considered statistically significant at the P value of <0.05.

RESULTS

At the end of the study, the number of rats in each group was like this: Control 10, zinc sulfate 10, zinc ethyl maltol 8, and zinc methyl maltol 9. After five weeks of feeding rats with zinc deficient diet, serum zinc concentration decreased to 50 ± 6 μg/dl and enzymes (ALP and LDH) activity to 42.5 ± 2 u/l and 47 ± 2 u/l, respectively. After this period of deficiency, Deficient rats were divided into four groups including: Control, zinc sulfate, zinc ethyl maltol and zinc methyl maltol. Three groups of rats were treated with drug solutions for two weeks. In this period, they received 2.5 mg zinc/Kg weight of rat daily. After 14 days of feeding drugs, serum zinc level and enzyme activity increased in all drug treated groups. According to Table 1, all groups were significantly different from control ($P = 0.0001$) in terms of serum zinc concentration and enzyme activity. Zinc methyl maltol differed significantly ($P = 0.0001$) from zinc sulfate. Serum zinc concentration and enzyme activity of zinc sulfate group were a little higher than that of zinc ethyl maltol but the difference was not significant ($P > 0.05$). Similarly, serum biochemical markers of zinc ethyl maltol group were higher than that of zinc methyl maltol group but the amount was not significant ($P > 0.05$).

DISCUSSION

Given the results of the study, serum zinc concentration of control was the lowest of study groups. Zinc is a part of lactic dehydrogenase and alkaline phosphatase and is necessary for the enzyme activity;[2,18] in other words, the more the zinc absorption, the more the enzymes activity; hence, due to the lowest serum zinc concentration, enzymes activity in dietary group was the lowest. This difference between dietary and drug treated groups shows that drug solutions increased serum zinc level and enzymes activity and thus improved zinc deficiency.

Results of the present study conforms to that of Ebrahimi's study in which intestinal absorption of zinc from drug solutions was measured *in vitro* by Everted Gut Sac (EGS) and compared with each other.[19] There was a significant difference between zinc sulfate and zinc methyl maltol in terms of serum zinc level and enzymes activity. It is so because absorption of zinc sulfate occurs through water channels while zinc methyl maltol is absorbed via integral proteins of cell membrane. Absorption through water channels is faster and better.[20]

There is one more alkyl group in ethyl maltol structure than methyl maltol which causes more lipophylicity and more intestinal absorption of ethyl maltol.[20] That is why zinc absorption in zinc ethyl maltol group was slightly more than zinc methyl maltol. Because of less zinc absorption in zinc methyl maltol group, enzymes activity was less.

Table 1: Comparison of the serum zinc concentration (μg/dl) and enzymes activity (u/l) of study groups at the end of the study

ALP	LDH	Zn	Groups
42.5±22	47±22	50±62	Control
73±51,2	76±31,2	87±71,2	Zinc methyl maltol
79±31	81±51	89±51	Zinc ethyl maltol
81±41	83±3.51	99±31	zinc sulfate

Significant difference with control (P=0.0001) Significant difference with zinc sulfate (P=0.0001)

CONCLUSION

According to the results of the study, it can be concluded that all of the mentioned drug solutions can increase serum zinc concentration and enzymes activity, but zinc sulfate and zinc ethyl maltol are more effective than zinc methyl maltol. Because of the mentioned reasons below, zinc ethyl maltol can be a preferable substitute for zinc sulfate to prevent and treat zinc deficiency:

- Similar effects of zinc sulfate and zinc ethyl maltol.
- Different effects of zinc sulfate and zinc methyl maltol.
- Zinc ethyl maltol does not cause gastrointestinal disorders.
- Zinc methyl and ethyl maltol are synthesized in almost the same way.

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