0148-0671/95/1905-0393$03.00/0
JOURNAL OF PARENTERAL AND ENTERAL NUTRITION

Vol. 19, No. 5
Printed in U.S.A

Effect of Intragastric pH on the Absorption of Oral Zinc Acetate and Zinc Oxide in Young Healthy Volunteers

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ABSTRACT. *Background:* Zinc is an important nutrient and is necessary to maintain a multitude of physiologic processes. Mineral supplements that provide physiologic doses of zinc may be used when dietary zinc is inadequate. Zinc is also used in pharmacologic doses to treat zinc deficiency and diseases such as Wilson's disease and acrodermatitis enteropathica. Although there are several zinc salts available, they are not equal in solubility, which is thought to be a key factor in zinc absorption. Moreover, the solubility of the salts is affected by pH, which may vary between pH 1 and 7 under various physiologic conditions in the stomach. The objectives of this 2-way 4-phase crossover study were to evaluate the effect of high (≥5) and low (≤3) intragastric pH on the absorption of zinc from the acetate and oxide salt in young healthy volunteers. *Methods:* After a 9-hour fast, 10 healthy subjects (5 males and 5 females) were given a single oral dose of 50 mg of elemental zinc as the acetate or the oxide salt and under either high or low intragastric pH conditions. In all phases, a Heidelberg capsule pH detector-transmitter was used to continuously monitor intragastric pH. During the high pH phases, single oral doses of famotidine 40 mg oral suspension were administered before the zinc to raise the intragastric pH above 5. Intragastric pH ≤ 3 was maintained in the low pH phases. *Results:* The mean plasma zinc area under the curve for zinc acetate at low pH (AL), zinc acetate at high pH (AH), zinc oxide at low pH (OL), and zinc oxide at high pH (OH) were 524, 378, 364, and 66 μg × h/dL, respectively. The highest zinc plasma concentrations occurred with the acetate salt at a low intragastric pH, while the lowest plasma concentrations occurred with the oxide salt at a high intragastric pH. The importance of pH to the dissolution of these salts was verified by *in vitro* tests. Twenty-four-hour urinary zinc excretion was the highest for the AL phase and lowest for the OH phase. *Conclusion:* This study indicates that intragastric pH and salt solubility-dissolution are important in the oral absorption of zinc. Specifically, the oxide salt is not an appropriate zinc salt to use in those patients with elevated intragastric pH. (*Journal of Parenteral and Enteral Nutrition* **19**:393–397, 1995)

Zinc, at required dietary concentrations, is important in the maintenance of homeostasis. If dietary zinc is inadequate, preparations containing physiologic doses of zinc may be used as a supplement. Zinc is also used in pharmacologic doses to treat disease. Zinc participates in many enzymatic processes involving bone formation, cell membrane stabilization, host defense, dark adaptation and night vision, and a variety of factors related to tissue growth. It is absorbed throughout the gastrointestinal (GI) tract with the highest rate of absorption occurring in the jejunum.[1] Failure to absorb adequate amounts of zinc can lead to zinc deficiency, which is manifested by growth retardation, hypogonadism, alopecia, skin lesions, diarrhea, mental depression, night blindness, altered taste sensation, impaired wound healing, and T-lymphocyte dysfunction.

Multivitamin and mineral preparations, which provide 4 to 15 mg of elemental zinc per dose, are often given to prevent zinc deficiency due to inadequate dietary zinc. The most commonly used zinc salt in these preparations is the oxide. In pharmacologic doses, Newsome et al[2] found zinc sulfate to be beneficial in the treatment of macular degeneration. These findings, although not confirmed, have prompted an increase in the use of zinc to treat this eye disorder of the elderly. Daily doses of up to 150 mg of elemental zinc as the acetate or sulfate salt are used to treat Wilson's disease.[3,4] Zinc is also used as a supplement in sickle cell disease and is used in the treatment of acrodermatitis enteropathica.[5]

The increasing use of zinc in the prevention and treatment of disease necessitates more definitive information regarding factors that may affect the absorption of various orally administered zinc salts. One factor that may be

Received for publication, June 27, 1994.
Accepted for publication, March 29, 1995.
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important in determining the extent of absorption is the solubility of the zinc salt used. The solubilities of the most frequently used salts vary from very soluble (sulfate and chloride) and freely soluble (acetate) to practically insoluble (carbonate and oxide).[6] Intragastric pH may also affect zinc absorption because insoluble zinc salts are solubilized by conversion to zinc chloride in the presence of gastric acid.

The effect of pH and dissolution on zinc absorption have not been well evaluated. Oelshlegel and Brewer[7] reported that plasma zinc concentrations after ingesting 25 mg of elemental zinc as the sulfate, acetate, or carbonate salt, did not differ significantly between the acetate and sulfate salts, but zinc absorption from the carbonate salt was significantly lower. Prasad et al[8] studied zinc absorption from the sulfate, acetate, and oxide salts (equivalent to 50 mg of elemental zinc) in 10 healthy volunteers . Like Oelshlegel and Brewer,[7] they found that zinc was absorbed to a significantly greater extent from the more soluble sulfate and acetate salts than from the practically insoluble oxide salt and that there was no difference in zinc absorption between the sulfate and acetate salts.

The degree of intragastric acidity may be an important factor affecting the absorption of zinc.[9] To date there has been only one published report investigating the role of gastric acid in zinc absorption. Sturniolo et al[10] studied the influence of gastric acid secretion on intestinal zinc (as the sulfate salt) absorption in healthy volunteers pretreated with oral histamine-2 receptor antagonists (H_2RAs), cimetidine and ranitidine. A statistically significant reduction in zinc absorption occurred after pretreatment with cimetidine and ranitidine when compared with no treatment. It was concluded that intragastric acid plays a role in the extent of zinc absorption in humans.

The objectives of the current study were to evaluate the effect of high ($\geq$5) and low ($\leq$3) intragastric pH on the absorption of zinc from the acetate and oxide salt in young healthy volunteers using continuous intragastric pH monitoring.

MATERIALS AND METHODS

Zinc Acetate and Oxide

Zinc acetate was selected because of its increased use as an alternative to the sulfate salt, which frequently causes dyspepsia and nausea. The acetate salt is currently used in the treatment of patients with Wilson's disease who take zinc to prevent copper reaccumulation.[4] Zinc oxide was selected because it is a salt frequently used by the pharmaceutical industry as a dietary supplement in multivitamin and mineral preparations. The acetate and the oxide salts also present useful contrasts in aqueous solubility, with the acetate salt being freely soluble and the oxide salt being practically insoluble.

Zinc acetate capsules, containing 50 mg (lot #9730) of elemental zinc, were provided by the Lemmon Company (Sellersville, PA). Zinc oxide capsules were prepared by the Investigational Drug Service at University Hospital using zinc oxide powder USP (Mallinckrodt, lot #8824KJSG), magnesium stearate NF (Lemmon Co, stock #4031), and corn starch (Redried Starch B) NF (Lemmon Co, stock #4111). The magnesium stearate NF and corn starch NF were provided by the Lemmon Company from stocks used to prepare zinc acetate capsules. This ensured identical inert ingredients in the zinc acetate and zinc oxide capsules. Zinc content was verified according to USP standards.

Volunteer Selection

Ten healthy volunteers, 5 females (20.4 $\pm$ 2.1 years of age, mean $\pm$ SD) and 5 males (23.8 $\pm$ 4.0 years of age, mean $\pm$ SD), participated in this study. All subjects were nonsmokers, within 20% of ideal body weight, and were judged to be in good physical condition on the basis of medical history, physical examination, blood chemistry, complete blood count, and urinalysis. Subjects were asked to refrain from taking any vitamin or mineral supplement 30 days before and during the entire study. None of the subjects were on any chronic medication with the exception of oral contraceptives. The participants were asked not to take any other medication or to consume ethanol 2 days before and during each treatment phase. The Institutional Review Board of the University of Michigan approved the study protocol and all subjects gave written informed consent. The study was conducted at the General Clinical Research Center (GCRC) at the University of Michigan Hospital.

pH Measuring System

A radiotelemetric device, the Heidelberg capsule (HC), was used to continuously determine intragastric pH. The details of this method have been previously described.[11] Briefly, the HC consists of a battery operated transmitter housed in an acrylic case about 7 $\times$ 20 mm. The battery was activated by immersion in normal saline the morning of each study. The capsule was calibrated immediately before the study, using pH 1 and 7 buffer solutions maintained at a temperature of 37°C. The capsule was tethered using surgical thread (Supramid Extra 2–0, S. Jackson Inc, Alexandria, VA) to ensure a fixed location of the capsule within the stomach during the study. The subject was asked to swallow the capsule with 90 mL of deionized water. If the subject had difficulty swallowing the HC, an additional 60 mL of water was administered. An antenna-receiver strapped around the midriff of the subject was used to detect the radio signal transmitted by the capsule, which is then converted to pH and recorded continuously as a function of time on an analog recorder. At the end of each study, the subject retrieved the HC orally and the capsule's response to pH 1 and 7 buffers were verified against prestudy values. The recalibration was required to be within 0.5 pH units of prestudy values for the results to be included in the analysis.

Experimental Design

The study was performed in a two-way crossover, four-phase design. The washout period between treatments was at least 7 days. The four phases were as follows: (1) zinc acetate administered to subjects pretreated with a single dose of famotidine 40 mg oral suspension (Pepcid oral suspension, Merck & Co, Inc, West Point, PA, lot #W0745) to raise the intragastric pH $\geq$ 5 (acetate high pH = AH), (2) zinc oxide administered to subjects pretreated with a single oral dose of famotidine 40 mg oral suspension to raise the intragastric pH $\geq$ 5 (oxide high pH = OH), (3) zinc acetate administered to subjects with an intragastric pH $\leq$ 3 (acetate low pH = AL), and (4) zinc oxide administered to subjects with an intragastric pH $\leq$ 3 (oxide low pH = OL). Each subject was given a single oral dose of either zinc acetate or zinc oxide equivalent to 50 mg of elemental zinc. The order of the two salts given was randomized. Subjects fasted from 9 PM the night before the first day of the study (day 1). Subjects came to the GCRC at 12 noon for lunch and 5 PM for dinner on day 1. After dinner the subjects were admitted as inpatients to the GCRC. Subjects were each given a snack to be eaten at 8:30 PM. They were instructed to fast throughout the day except for water, which could be taken as desired, and the scheduled meals. On day 2 of the study, an indwelling catheter was inserted into a forearm vein and approximately 5 mL of blood was collected at 6 AM for baseline zinc concentration. The tethered HC was then swallowed with 90 mL of deionized water and its position was fixed by taping the tether thread to the subject's cheek after the capsule had traveled at least 45 cm. Correct capsule position in the stomach was verified by a combination of tether length and a pH of <3 for at least 10 minutes.

High intragastric pH studies. Famotidine was selected because of its potent inhibitory effects on gastric acid and because it does not contain an imidazole group that has been shown to be a zinc ligand.[12] The imidazole portion of drugs such as cimetidine and omeprazole have the potential to increase zinc absorption.

During the high intragastric pH ($\geq$5) phases, subjects received 40 mg of famotidine oral suspension with 60 mL of deionized water. After 45 minutes an additional 60 mL of water was given. Water administration was repeated every 15 minutes until the pH remained above 5 for at least 10 minutes. A dose of zinc acetate or zinc oxide equivalent to 50 mg of elemental zinc was then administered with 120 mL of deionized water. Just before zinc administration a 24-hour urine collection

was begun. Intragastric pH was monitored for 4 hours after zinc administration. To meet the study criteria, the pH had to be ≥5 for at least 80% of the first hour after zinc administration. Beginning 1 hour after the administration of the zinc dose, 5 mL of blood was collected hourly for 8 hours. Four hours after zinc administration, the HC was retrieved orally by the subject and the capsule was recalibrated. Each subject consumed the same lunch and dinner, as on day 1, at 4 and 8 hours after zinc administration. After dinner, the subjects were permitted to leave the GCRC and were given a snack to be consumed at 8:30 PM. Subjects returned to the GCRC at a predetermined time on day 3 to complete the after zinc administration 24-hour urine collection.

Low intragastric pH studies. The same procedure as outlined above was followed for the low pH phase of each zinc salt, except that famotidine was not administered. The low pH phase followed the high pH phase so that the water consumption could be duplicated. For the low pH criteria to be met, the pH had to be ≤3 for at least 80% of the first hour after zinc administration.

Diet

During each treatment phase, the subjects consumed a eucaloric diet that had a calculated value of 18 mg of zinc per day. The Food Processor II Nutrient & Diet Analysis System software (ESHA Research, Salem, OR) was used to calculate the diet and determine energy needs for each subject. The daily study diet consisted of a total of 720 mL of Ensure Plus (Ross Laboratories, Columbus, OH), 180 g turkey, 90 g ham, 135 g white bread, 42 g mayonnaise, 30 g lettuce, and 56 g potato chips. Varying gram weights of a lemon-lime carbonated beverage and gumdrop candy were given to make eucaloric adjustments for each subject. Deionized water was consumed by the subjects during confinement in the GCRC. Subjects were allowed to consume tap water at all other times during the study.

Sample Collection and Analysis

All blood samples were collected in syringes containing zinc-free heparin and immediately transferred to zinc-free tubes (Falcon, Becton Dickinson, Lincoln Park, NJ). The samples were centrifuged at 3000 rpm for 10 minutes at 4°C. Plasma fractions were transferred to zinc-free tubes (Falcon, Becton Dickinson) and stored at -20°C until analysis. Urine was collected in EDTA-washed gallon containers. At the end of each 24-hour collection, the urine volume was measured and aliquots were stored in polypropylene tubes with screw caps (Centrifuge Tubes, Elkay Products, Inc, Shrewsbury, MA) at -20°C until analysis.

Plasma and urinary zinc were determined by flame atomic absorption spectrophotometry (AAS) (model 451; Instrumentation Laboratory, Wilmington, MA). Plasma zinc was determined after diluting (1:10) the samples in 0.5% trace element–free nitric acid. Standards were run every five samples.

Data and Statistical Analysis

Plasma zinc concentrations for hour 1 through hour 8 were adjusted for baseline zinc concentration by subtracting the hour 0 concentration value. When this difference was less than 0, the baseline adjusted value was set at 0. Total zinc concentration at each dose for each subject was measured by plasma zinc area under the concentration versus time curve (AUC) formed by the baseline adjusted values from hour 0 through hour 8. Plasma zinc AUC was calculated using the trapezoidal rule method[13] as implemented in the TRAP function available in the BMDP statistical software package (BMDP statistical software manual to accompany the 1990 software release, W J Dixon, M B Brown, L Engelman, et al. Berkeley: University of California Press, 1990).

Repeated measures analysis of variance (ANOVA) was used for both plasma concentration and urinary content to test the null hypothesis that mean zinc levels for plasma or urine were the same for all four treatment groups. The alternative hypothesis is that at least one group was different from the others. Program 2V in BMDP was used for the repeated measures ANOVA. BMDP was run on a VAX 4000-200 computer.

In Vitro *Studies*

Dissolution tests were conducted in a rotating basket apparatus[14] to determine the effect of salt and pH on the dissolution of zinc from zinc acetate and zinc oxide capsules. Capsules were placed in baskets and rotated at 50 rpm at 37°C in 900 mL of water. Simulated Gastric Fluid USP (SGF, without pepsin), and Simulated Intestinal Fluid USP (SIF, without pancreatin). The SGF had a pH of approximately 1.2 and the SIF had a pH of approximately 7.5. These fluids were chosen to model the stomach under normal fasting conditions (SGF) and under achlorhydric conditions (SIF). Dissolution of capsules was studied in duplicate in each medium. Ten-milliliter samples of fluid were taken every 15 minutes for 2 hours, with volume replacements, and the samples were assayed for zinc content by AAS. *In vitro* samples were collected in zinc-free tubes (Falcon, Becton Dickinson) and stored at -20°C until analysis.

RESULTS

The in vitro dissolution results (Table I) indicate that in both water and SIF (pH ≅ 7.5), zinc oxide dissolves very slowly. At the lower pH of SGF (pH ≅ 1.2), both salts showed increased dissolution, with the effect more pronounced for the oxide.

Two subjects maintained intragastric pH 3 during 78% of the first hour instead of 80%, in one of the two high pH phases. The data were included in the analysis because of the small difference.

Figure 1 illustrates the unadjusted mean plasma zinc concentration curves. Unadjusted means and standard deviations for plasma zinc AUC (PZAUC) for each treatment are reported in Table II. The data show that the highest plasma zinc concentration occurs with the acetate salt at low intragastric pH (AL) and the lowest plasma zinc concentration occurs when the oxide salt is given at the high intragastric pH (OH). The plasma zinc concentrations produced by the administration of the acetate salt during the high intragastric pH phase (AH) and the oxide salt during the low intragastric pH phase (OL) are essentially equivalent.

These plasma results are corroborated by the urine results, which are shown in Figure 2 and Table III. The highest urinary zinc content occurs with the acetate salt at low intragastric pH (AL) and the lowest urinary znc content occurs with the oxide salt at high intragastric pH (OH), while the acetate salt at high intragastric pH (AH) and oxide salt at low intragastric pH (OL) are essentially equivalent.

Statistically, the ANOVA indicated a significant difference between treatments with respect to PZAUC ($p < .05$). The ANOVA also indicated an interaction between salt and pH ($p < .05$) in their affect on plasma concentration. Pairwise post-hoc comparisons using the method of Student-Newman-Keuls (SNK) detected a significant difference between the oxide salt at high intragastric pH (OH) phase and each of the three other phases ($p < .05$).

TABLE I
Dissolved zinc in water, simulated gastric fluid, and simulated intestinal fluid

	Initial content*	Fluid	1 hour (mg)	2 hours (mg)
Zinc salt				
Zinc acetate	(50 mg)	Water	36.7 (73)	43.7 (87)
		SIF†	44.9 (90)	37.4 (75)
		SGF‡	43.7 (87)	46.5 (93)
Zinc oxide	(50 mg)	Water	0.5 (1.0)	0.6 (1.2)
		SIF	0.6 (1.2)	0.5 (1.0)
		SGF	39.2 (78)	41.0 (82)

Values in parentheses are percentages.
*Capsules (n = 2) contained 50 mg elemental zinc.
†Simulated Intestinal Fluid, USP, without pancreatin.
‡Simulated Gastric Fluid, USP, without pepsin.

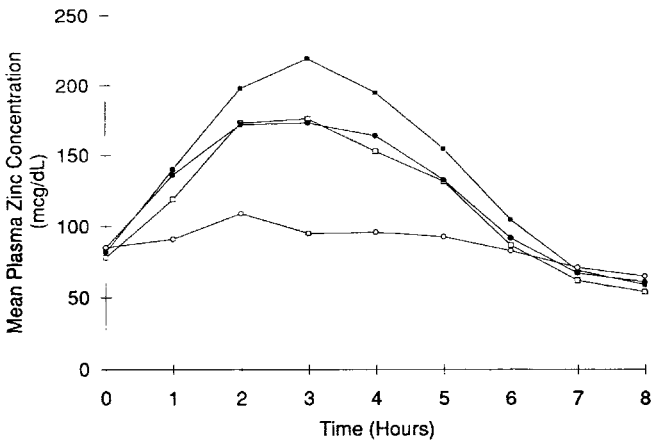

FIG. 1. Mean plasma zinc response over time to zinc acetate and zinc oxide administration at low (≤3) intragastric pH and high (≥5) intragastric pH (n = 10). ■, zinc acetate at low pH(AL); □, zinc acetate at high pH(AH); ●, zinc oxide at low pH (OL); ○, zinc oxide at high pH (OH).

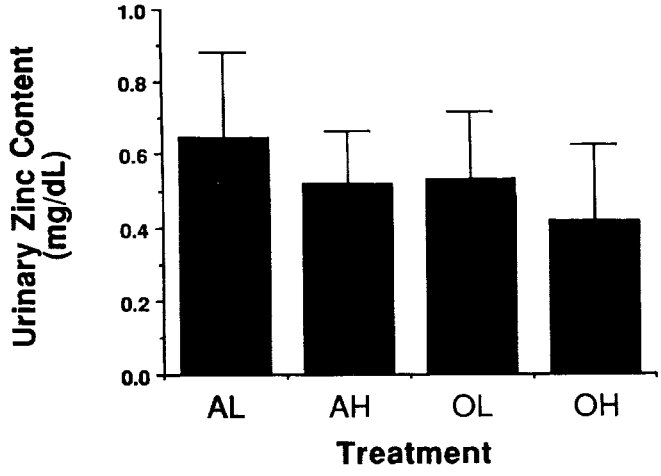

FIG. 2. Mean 24-hour urinary zinc excretion in response to zinc acetate and zinc oxide administration at low (≤3) intragastric pH and high (≥5) intragastric pH (n = 8). AL, zinc acetate at low pH; AH, zinc acetate at high pH; OL, zinc oxide at low pH; OH, zinc oxide at high pH. AL is significantly different from OH ($p < .05$).

TABLE II
Unadjusted plasma zinc AUC values corresponding to low (≤3) and high (≥5) intragastric pH

	Zinc acetate	Zinc oxide
Low pH	524 ± 112	364 ± 152
High pH	378 ± 126	66 ± 35*

Values are means ± SD expressed as μg × h/dL; number of subjects = 10.
*Significantly different ($p < .05$) from zinc oxide at low pH (OL), zinc acetate at low pH (AL), and zinc acetate at high pH (AH).

TABLE III
Unadjusted urinary zinc content values of zinc acetate and zinc oxide corresponding to low (≤3) and high (≥5) intragastric pH

	Zinc acetate	Zinc oxide
Low pH	0.649 ± 0.233	0.536 ± 0.183
High pH	0.521 ± 0.146	0.422 ± 0.209*

Values are means ± SD expressed as mg/d; number of subjects = 8.
*Significantly different ($p < .05$) from zinc acetate at low pH (AL).

The ANOVA also showed that there was a significant difference between treatments with respect to urinary zinc content (UZC, $p = .01$). SNK detected a significant difference between the acetate salt at low intragastric pH (AL) and oxide salt at high intragastric pH (OH) phases ($p = .05$).

Nausea occurred more frequently with the acetate salt than with the oxide salt. Fifty percent of the subjects reported nausea during the low pH zinc acetate phase, 70% experienced nausea during the high pH zinc acetate phase, 20% reported nausea during the low pH zinc oxide phase, and only 10% were nauseated during the oxide salt at high intragastric pH phase. The mean duration of nausea and mean time of onset after the zinc dose was 40 and 80 minutes, respectively.

DISCUSSION

The important findings in this study are as follows: (1) gastric acidity enhances zinc absorption; (2) zinc from the oxide salt is absorbed to a lesser extent than zinc from the acetate salt; and (3) zinc absorption from the oxide salt in a high intragastric pH environment is less than what would be expected given the individual effects of the oxide salt and high intragastric pH.

In vitro data suggest that the likely mechanisms for these findings are the aqueous solubility of the salt and the effect of pH on dissolution. Zinc oxide is practically insoluble at a high intragastric pH and the dissolution of zinc oxide at this pH is extremely low (Table I). Thus, in the absence of gastric acidity, a zinc oxide capsule would not be expected to dissolve well in either the stomach or the intestine, and therefore zinc would not be well absorbed. This is demonstrated in the *in vivo* OH data in Tables II and III, and Figures 1 and 2. In the presence of gastric acidity zinc oxide is partially solubilized (Table I) and therefore has greater absorption than at a high intragastric pH (OL vs OH: Tables II and III, and Figures 1 and 2).

In vitro data also support the hypothesis that gastric acidity enhances the solubility and dissolution of the acetate salt (Table I). The result, as demonstrated in the in vivo data, is an increase in zinc absorption (AL *vs* AH: Table II and Figure 1). These results are similar to the results of the 24-hour urinary zinc content found in Table III and Figure 2.

The clinical implications of these findings are important because many of the patients taking zinc for the prevention or treatment of disease are in the older age group. The incidence of hypochlorhydria in patients over age 60 years is estimated to be 31%, with achlorhydria in this age group estimated at 5% to 10%.[15] Other patient populations likely to have high intragastric pH (pH ≥ 5) include those taking antacids or gastric acid inhibitors, those with pernicious anemia, and patients with AIDS. The results of this study indicate that there is a risk of decreased zinc absorption when zinc oxide is used in patients with elevated intragastric pH.

Well-designed studies that have evaluated the effect of altered intragastric pH on zinc absorption are lacking in the literature. To our knowledge the study by Sturniolo et

al,[10] using the sulfate salt, is the only published report that investigated the *in vivo* effects of gastric acid inhibition on zinc absorption.[10] No published data appear to be available concerning the effects of gastric acid inhibition on the absorption of zinc from the oxide and acetate salts.

Sturniolo and colleagues[10] found that in healthy volunteers, the pharmacologic inhibition of gastric acid secretion significantly reduced the absorption of zinc from an orally administered zinc sulfate (equivalent to 50 mg of elemental zinc). In one group, zinc absorption was determined after an oral dose of zinc sulfate with and without pretreatment with cimetidine. The zinc AUC was significantly decreased after cimetidine compared with no pretreatment. A second group received zinc sulfate after pretreatment with ranitidine and cimetidine, and with no pretreatment. In this group, intragastric acidity was measured hourly for 6 hours using a nasogastric tube. Ranitidine, but not cimetidine, significantly increased intragastric pH compared with no pretreatment. In addition, a statistically significant reduction in zinc absorption was reported after ranitidine.

There are several concerns with Sturniolo's study design. First, the imidazole group on the cimetidine molecule has been shown to be a zinc ligand[12] and may increase zinc absorption. By using famotidine, which has not been shown to interact with zinc, it was possible to better quantitate differences in absorption between low and high intragastric pH conditions.

Second, the method and frequency of intragastric pH monitoring that Sturniolo used was unclear. The method of measuring intragastric pH is critical, because intragastric pH may fluctuate widely over time.[11] The preferred method for measuring intragastric pH is continuous monitoring, rather than on an hourly basis. By using the Heidelberg capsule technique, a continuous monitoring method, we were able to closely monitor the pH during the absorptive phase. In our study, the pH values required for the low (≤ 3) and the high (≥ 5) intragastric pH phases were maintained during at least 80% of the first hour after zinc administration, thus assuring that the zinc would be in the appropriate pH environment during the absorptive phase.

Despite the pitfalls of the Sturniolo study,[10] our results are consistent with theirs. Although Sturniolo used zinc sulfate and we used zinc acetate, these salts have similar solubilities and therefore similar results would be expected.

It is interesting to note that the incidence of nausea was the greatest during the acetate salt phases. The mechanism for this adverse event is unclear, but may be due to local irritation.

In conclusion, this study indicates that the oxide salt is not an appropriate zinc salt to use in those patients who are hypochlorhydric or achlorhydric. Zinc acetate was absorbed more consistently and is the preferred zinc salt to use in patients with AIDS, pernicious anemia, in patients on gastric acid inhibitors, and in the elderly.

ACKNOWLEDGMENTS

We thank Robert Dick for assistance in sample analysis and Veroncia Vick for assistance in the *in vitro* studies. Data was analyzed by Daniel J. DuRoss, MS, Systems Manager, General Clinical Research Center, University Hospital, and reviewed by Morton B. Brown, PhD, Professor of Biostatistics, School of Public Health, University of Michigan, Ann Arbor. This work was supported by The University of Michigan College of Pharmacy Upjohn Research Award; the Biomedical Research Support Grant 2S07-RR05571–28, Department of Health and Human Services, US Public Health Service; and by the General Clinical Research Center (GCRC) at the University of Michigan Grant M01-RR00042 from the National Center for Research Resources, National Institutes of Health, USPHS. LMH was supported by a Glaxo Research Fellowship.

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