Chapter 9

ZINC

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I. Product Information

A. Introduction

Zinc participates in metabolism in three principle areas: 1) as a component of zinc metalloenzymes such as alcohol dehydrogenase, carbonic anhydrase, DNA polymerase, etc.;[1] 2) as a stabilizer of polysomes during protein synthesis;[2] and 3) as a stabilizer of cell membranes, particularly of circulating cellular elements.[3] The physiological functions of zinc in humans that are dependent on an adequate zinc nutriture include: cell growth and proliferation; sexual maturation and reproduction; dark adaptation and night vision; gustatory acuity; wound-healing; and host immune defenses. A number of diseases for which TPN is indicated (Crohn's disease, short-bowel syndrome, etc.) predispose to a pre-existing deficiency of zinc, and instances of zinc deficiency during TPN have been reported

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frequently. Both nitrogen retention and insulin secretion are improved when subjects undergoing TPN are maintained in positive zinc balance.[4] Moreover, in the nutritionally-depleted patient, additional requirements for zinc for new growth of tissue are present. Thus, zinc should be included routinely in regimens of total parenteral nutrition.

B. Chemistry

Zinc has an atomic number of 30, and an atomic weight of 65.37. Zinc is highly soluble in its ionic form throughout a wide range of pH. It is stable in the divalent, Zn(II), oxidation state. Zinc can form soluble complexes with organic anions such as amino acids (notably histidine and cysteine). It forms insoluble precipitates with dietary substances such as phytic acid, but it is unlikely that any routine component of an intravenous solution would form insoluble complexes with zinc.

C. Dosage Forms/Concentrations/Manufacturers

The general guidelines for the administration of zinc and the remaining trace minerals to be discussed in this section are derived from the recommendations (1979) formulated by an ad hoc expert panel of the American Medical Association.[5] The AMA panel suggested that individual trace element solutions contain ionic zinc at a concentration of 1.0 mg/ml. The preferred salt is zinc sulfate ($ZnSO_4 \cdot 7H_2O$; mol wt 287.56), containing 22.74% Zn(II). A concentration of the sulfate salt of 4.39 mg/ml would constitute the recommended dosage. An extensive, but not necessarily exhaustive, list of sterile trace mineral additives available commercially is included in Table I.

D. Uses/Functions

Intravenous zinc additives are used to cover the usual deficit in daily delivery of this trace mineral during TPN, since most crystalline amino acid solutions, lipid emulsions and vitamin additives combined provide less than the maintenance requirements of zinc.[6, 7] These products are used, therefore, for the maintenance of adequate zinc nutriture during the duration of TPN, and for repletion should a zinc deficiency be present (as commonly is the case) when intravenous nutrition is begun. In both exclusively parenteral and mixed parenteral-plus-oral regimens, the use of intravenous zinc is advisable since the intestinal absorption of zinc, especially by the compromised small bowel,[8] is generally not an efficient process, and since any diarrheal fluid losses provoked by the oral intake are likely to increase overall zinc requirements.[4] Maintenance of positive zinc balance is an essential prerequisite to a vigorous anabolic response in the protein-energy depleted patient[4] and zinc availability may determine the nature and composition of the weight gained during nutritional repletion.[9] Because of its role in growth and development, zinc nutrition is extraordinarily important to infants and children, and especially to premature infants subjected to TPN prior to full intrauterine maturation.[10]

TABLE I. Commercially Available Zinc Products

Product	Manufacturer	Type of Salt	Ionic Conc. (mg/ml)	Container
Zinc Chloride, USP	Abbott	Chloride	1	10 ml vl.
Zinc Chloride	Abbott	Chloride	1	50 ml MDV
Zinc Trace™	Armour	Chloride	1	10 ml vl.
Zinc Sulfate, USP	LyphoMed	Sulfate	1	10, 50, 100 ml vls.
Zinc Sulfate	LyphoMed	Sulfate	1	30 ml MDV
Zinc Sulfate	LyphoMed	Sulfate	5	10 ml vl. (concentrate)
Zinc Sulfate, USP	Pasadena	Sulfate	1	30 ml vl.

II. Professional Implications

A. Preparation/Compounding/Analysis/Synthesis

Unlike the organic micronutrients, issues of preparation, compounding and synthesis are relatively straightforward and trivial for the minerals since pure and ultrapure forms of the respective, designated salts are available. The salts have been recommended on the basis of stability and solubility characteristics, and at issue are the careful measurement and sterilization of the additive solutions. As stated, zinc sulfate is the most widely recommended zinc compound for use in intravenous solutions. Concentration of zinc in solutions can be measured readily by atomic absorption spectrophotometry (AAS). The concentrations that should be present for maintenance are detectable by most instruments. Unsupplemented solutions may have concentrations below the detection limits of AAS, and some concentration of the solution by evaporation may be required. From a nutritional standpoint, however, precise and accurate determination of zinc in subthreshold concentrations is unproductive since it should be evi-

dent that the regimen could not supply the necessary mineral. Only in rare cases of zinc overload would such analyses be indicated. With zinc, and indeed all of the trace minerals, the potential for exogenous contamination of a fluid sample is great given the ubiquitous nature of the mineral. In all phases of sample handling, preparation and analysis, strict precautions for trace-mineral-free materials, thoroughly washed and rinsed, and preferably of plastic, should be maintained. Erroneously high results in determinations of zinc in solutions can be deceptive to the practitioner, and potentially injurious to the patient who will be thought to be receiving more of the mineral than he or she will in actuality obtain.

B. Antagonists/Inhibitors/Potentiators/Synergistic Agents

Zinc and copper compete for intestinal uptake. It is not known whether this competition becomes manifest at any postoperative site, but it is important to note that the Zn:Cu ratios in TPN solutions—2:1 to 4:1—are lower than those generally found in the usual diet. Since zinc plays a major role in protein synthesis and cell growth, the availability of amino acids in the TPN solutions potentiates these actions of zinc.

C. Contraindications/Precautions/Warnings

Parenteral zinc should not be administered to individuals suspected of having a pre-existing zinc toxicity; such individuals, however, are rarely encountered. The administration of routine maintenance doses of zinc in TPN is no guarantee that zinc deficiency will be prevented, and does not eliminate the responsibility for monitoring zinc status initially and periodically during the course of TPN.

D. Pharmacokinetics/Disposition

1. Bioavailability/Absorption

Although a number of factors influence the bioavailability of dietary zinc, parenterally administered zinc is highly available to the body. In the treatment of zinc deficiency syndrome with therapeutic doses of parenteral zinc, clinical responses — reversal of deficiency manifestations such as behavioral changes and skin lesions — have been obtained within 2-7 days,[11] and some observers have reported a response within 24 hours.[12] Ladefoged[8] showed a 61% retention of infused zinc in patients with severe short-bowel syndrome.

2. Distribution/Binding

Under usual circumstances, the fully zinc-replete adult contains 2 to 3 g of zinc.[13] About 20% of body zinc is in the skeleton, a pool which is not readily mobilized for use during periods of deficient zinc intake, except

when bone is being actively reabsorbed. The liver has a zinc concentration of 55 ug/g. In an adult man, this would represent 1.5 g. Tissue levels generally range from 20 to 400 ug/g with pancreas, retina and gonadal tissue having higher concentrations (600-800 ug/g).[13] Between 3 and 4 mg of zinc are present in the cell-free portion of the systemic circulation. Under normal conditions, this is equivalent to a plasma concentration of 70 to 130 ug/dl. Forty percent is tightly bound to an alpha$_2$-macroglobulin (a zinc metalloprotein) fraction of serum proteins, and is not available for nutritional or metabolic uses. About 55% is loosely bound to albumin; this appears to be the nutritional transport fraction. The other 5% of zinc is associated with free amino acids and other low-molecular-weight species in the plasma. This fraction represents the zinc filterable by the kidneys (500 ug to 1 mg/d excreted). The albumin of patients with alcoholic cirrhosis has a decreased affinity for zinc.[14]

3. Blood Levels

In healthy individuals, plasma zinc levels range from 70 to 130ug/dl. Numerous physiological factors influence circulating zinc levels, including short-term fasting and tissue necrosis (which increase zinc concentrations), and corticosteroid therapy, exogenous estrogens, and pregnancy (which decrease zinc concentrations).[15] Infectious or inflammatory stress will mediate a major, acute sequestration of circulating zinc by the liver, producing up to a 50% decline in plasma zinc concentrations. In the determination of zinc concentrations, external contamination of glassware or plastic ware, hemolysis, and prolonged venous occlusion during venipuncture can all falsely elevate zinc levels. Hypoalbuminemia is associated with hypozincemia, and a familial hyperzincemia, due to a genetic variation in the binding-affinity of albumin, has been described.[16]

4. Metabolism

The storage sites for the metabolically-active zinc in the body are liver and, most probably, skeletal muscle. The biological half-life of radioactive zinc traces in man is over 500 days.[17] At the cellular level, zinc participates in zinc metalloenzymes, in protein synthesis and in membrane conformation.

5. Excretion

The normal route of excretion of zinc from the body is via the intestinal tract, largely in meal-stimulated pancreatic secretions.[18] Bile and intestinal secretions also contribute to endogenous losses in feces. In the absence of oral intake, there is atrophy of intestinal mass and pancreatic biliary secretion volumes are reduced; this could potentially reduce the capacity of the body to excrete zinc by way of the usual routes and aid retention of this mineral during TPN. Renal excretion usually accounts for only a small fraction of daily zinc losses. In a healthy adult, about 500 ug of zinc will be ex-

creted in the urine daily. Urinary losses of zinc are usually elevated in patients undergoing TPN. This could be a consequence of the elevation of free amino acids, alterations in hormonal rhythm, or an adaptive response to the reduced stimulation of the alimentary tract secretions. Superficial losses of zinc from the outgrowth of hair, desquamation of epidermal cells and sweating account for the loss of 0.5 to 1.5 mg of endogenous zinc daily. Increased sweat losses in the febrile patient can increase the surface loss of zinc by two- or three-fold.

III. Patient Considerations

A. Administration

Zinc additives should be diluted, usually by adding the appropriate amount of zinc from a 1 mg/ml stock solution (Table I) to one of the daily infusion solutions of a 500 to 1000 ml volume. It can be added alone or as part of a multi-element preparation. The AMA expert committee[5] was emphatic in suggesting that only single-entity preparations be formulated, based on the assumption that patients might have differential requirements for the four specified trace elements depending on their disease status and nutritional status. Nonetheless, as shown in Appendix A-General Tables, many manufacturers have provided multi-element trace mineral additives, and their use has become quite popular. For routine replacement in the stable patient, the multi-element formulations are convenient, but when specific manipulation of zinc dosage is required, additional zinc must come from a single entity solution of zinc, distributed over the various daily infusion containers. Concentrations of zinc in infusates should not exceed 10 mg/L unless the total parenteral requirement for the given patient is greater than 30 mg.

B. Adverse Reactions

No adverse reactions to the established therapeutic maintenance dosages of parenteral zinc are known. Allergic reactions are also unknown. Toxic reactions to overdoses of parenteral zinc have been recognized (see Sec. III-G).

C. Monitoring

Nutritional status with respect to zinc should be monitored faithfully and frequently in patients undergoing TPN. A wide range of options for assessing human zinc status has been published (Table II), but none of these indices is an unequivocal indicator of total-body zinc status, and with several

TABLE II. Laboratory and Diagnostic Options for Assessing Human Zinc Status

circulating (plasma/serum) zinc concentration*
red cell zinc content
leukocyte zinc content
platelet zinc content
salivary zinc concentration
hair zinc content
24-h urine zinc excretion*
urinary zinc/creatinine ratio
serum alkaline phosphatase*
erythrocyte carbonic anhydrate
erythrocyte nucleoside phosphorylase
serum ribonuclease (RNAase)
taste acuity
dark adaptation
neutrophil/macrophage chemotaxis
in vitro red cell zinc-65 uptake
oral zinc tolerance test†
platelet aggregation tests†
delayed cutaneous sensitivity response†

*of particular utility in TPN patient evaluations.
†requires further experience and validation in humans.

there are specific pitfalls of interpretation in patients undergoing TPN. Hypoalbuminemia, for instance, is common in malnourished patients and will lower zinc concentration in serum even in the presence of adequate stores. During acute infections, leukocytic endogenous mediators (LEM) cause the redistribution of zinc from the circulation to the liver.[19] However, in stable, afebrile patients receiving unsupplemented TPN solutions followed longitudinally, an average decline in zinc concentrations of -5 to -7 ug/dl/week was observed by two independent series.[20, 21] Thus, under constant conditions, circulating zinc can be a useful guide to zinc status. However, in a recent report of serial monitoring patients on TPN receiving zinc supplements,[22] circulating zinc values remained stable despite negative zinc balance in some patients. However, these investigators reported that a direct relationship was observed between zinc

TABLE III. Common Diseases and Situations Predisposing to Zinc Deficiency

Acrodermatitis enteropathica
Alcoholism
Alcoholic cirrhosis
Alcoholic pancreatitis
Anorexia nervosa
Celiac disease
Cystic fibrosis
D(−) penicillamine
Inflammatory bowel disease
Jejunoileal bypass
Nephrotic syndrome
Pancreatic insufficiency
Pica
Pregnancy
Prematurity
Short-bowel syndrome
Sickle cell anemia
Thalassemia
Thermal burns
Uremia

infused and zinc excreted in urine over a range of zinc dosages.[22] Confounding variables in the amino acid composition of the TPN solutions (or the ethanol content of some European regimens) could influence differential excretion of zinc in urine. In a number of reports, some from areas of the world where zinc determinations were unavailable, alkaline phosphatase has proven to be a good index of zinc deficiency in patients on TPN, increasing to normal levels with zinc supplementation.[23] A number of the functional indices of zinc status cited within the General Tables have potential for use in monitoring zinc status. Their prospective applications in TPN patients deserve evaluation.

D. Expiration

The expiration date accompanying the commercially available product should be noted; however, once opened, the vial may be used up to 24

hours if kept in a laminar flow environment. The expiration date of TPN solutions that contain zinc should be designated as 24 hours unless other information has been determined. It should be remembered that Maillard reaction products may chelate trace elements.

E. Storage

Most trace mineral additives do not contain bacteriostatic agents. In spite of the fact that trace elements may act as a preservative, the vials should be discarded after a single use. The unopened commercially available products may be stored at room temperature.

F. Requirements/Deficiencies

TPN solutions, unsupplemented with zinc, have variable concentrations of the mineral, ranging from 20 to 2800 ug/L.[7] Protein hydrolysates tend to have a higher intrinsic concentration, but the crystalline amino acid solutions more commonly in use today generally have a low concentration of zinc. Evidence from a number of quarters demonstrates that patients receiving TPN not supplemented with zinc will be in negative zinc balance.[4,24-26] The AMA expert committee recommendations are listed in the Appendix A, General Tables. They take into consideration the fact that zinc is laid down in the fetus toward the end of gestation and, thus, premature infants require larger amounts (300 ug/kg) to make up for the failure of maternal-fetal transfer than full-term and older children (100 ug/kg). Stable adults require 2.5 to 4.0 mg according to the AMA committee. Lowry et al.[26] have determined that for tumor-bearing adults, a 70 to 80 ug/kg daily parenteral infusion of zinc was associated with hormal blood levels and positive zinc balance. This would be the equivalent to 4.9 to 5.6 mg in the 70 kg patient. Acute catabolic stress obligates addition of 2 mg above the basal requirements. Interestingly, intestinal fluid losses produce massive wastage of zinc.[4] Thus, the replacement of zinc for individuals with ileostomy or diarrheal fluid output of several liters per day will require large doses of parenteral additive zinc.

had been included in the regimen. Susceptibility to zinc deficiency during TPN may be, in part, conditioned by the fact that many diseases and conditions predispose to zinc depletion (see Table III). The clinical manifestations of zinc deficiency in humans are listed in Table IV. Certain signs — growth retardation, delayed sexual maturation — are seen only in children. Most of the remaining manifestations of zinc deficiency listed were seen in the first cases of TPN-associated zinc deficiency reported.[12] It is important to note that diarrhea will persist even in the absence of oral intake when it is due to zinc deficiency.[36] The skin lesions of acute zinc deficiency deserve special note since they often mimic the lesions of acroder-

TABLE IV. Clinical Manifestations and Consequences of Zinc Deficiency

Growth retardation
Hypogonadism
Hypospermia
Alopecia
Skin lesions
Diarrhea
Mental depression/apathy
Glucose intolerance
Night blindness
Impaired taste sensation/perception
Impaired wound healing
Impaired white cell chemotaxis
Impaired T-lymphocyte function
Cutaneous anergy

matitis enteropathica, the inheritable zinc-deficiency syndrome. However, all variety of skin lesions — papular, pustular, eczematoid, acneiform and seborrheic — have been produced in TPN-induced deficiency of zinc. Other nutrient deficiencies — notably, of biotin and essential fatty acids — also produce skin lesions and are also seen during TPN.

G. Dose (Treatment/Toxicity)

Treatment of zinc deficiency requires an increment of the parenteral zinc dosage, up to 10-fold. If infused steadily over the course of 24 hours, dosages of 50 to 100 mg daily can be tolerated. Oral zinc has also been used in TPN patients. Toxic manifestations from excessive intravenous zinc range from mild to lethal. In Brazil, a 10-fold error in formulation of parenteral infusates — 23 mg rather than 2.3 mg of zinc added to each ration — resulted in asymptomatic hyperamylasemia.[37] Infusion of 9.8 mg of zinc over a one-hour period produced transient flushing, blurred vision, and sweating.[38] A death occurred in a 72-year-old woman 47 days after she inadvertently received 1.6 g of zinc intravenously as a consequence of an error in home dialysis. Acutely, zinc concentrations rose to 4184 ug/dl, or 40 times the normal level. Hyperamylasemia, cholestatic jaundice, anemia and thrombocytopenia developed prior to her demise.[39]

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