PRODUCT MONOGRAPH

M.T.E.-4 AND M.T.E.-4 CONCENTRATED

Multi-Trace Element

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NAME OF DRUG

M.T.E.-4 AND M.T.E.-4 CONCENTRATED

THERAPEUTIC CLASSIFICATION

Multi-Trace Element

ACTIONS AND CLINICAL PHARMACOLOGY

Zinc

Zinc is an essential nutritional element that plays a key role as a component of numerous metalloenzymes such as carbonic anhydrase, alkaline phosphatase, lactic dehydrogenase and carboxypeptidase. At least one zinc metalloenzyme has been identified in each of the six major categories of enzymes; i.e., oxidoreductase, transferase, hydrolase, lyase, isomerase and ligase. Zinc is also necessary for the synthesis of RNA and DNA, making it important in the normal growth and development process. Zinc helps maintain normal skin hydration and the senses of taste and smell and facilitates wound healing.

Zinc resides in muscle, bone, skin, kidney, liver, pancreas, retina, prostate and particularly in red and white blood cells. Calculations from data indicate that 75 to 88% of the total zinc of normal blood is contained in red cells (primarily in the zinc metalloenzyme carbonic anhydrase), 12 to 22% in the plasma and 3% in the leukocytes. Normal plasma levels of zinc vary from approximately 88 to 112 μg/100 mL. Practically all zinc in serum is protein bound including plasma albumin, α_2-macroglobulin and some plasma amino acids including histidine, cysteine, threonine, glycine and asparagine. Infection influences the uptake of zinc by the liver and reduces plasma concentration. This process is stimulated by leukocyte endogenous mediator (LEM).

Absorption of zinc occurs mainly in the small intestine, predominantly in the duodenum. The primary excretory pathway for zinc is the feces and pancreatic secretion. The largest component comes from direct transfer of zinc through the intestinal wall. Several researchers showed that diarrhea, stomal and fistula losses were major sites of abnormal losses of zinc from endogenous sources in patients receiving TPN

solely. Small amounts of zinc may be lost in the urine (300-700 μg per 24 hrs). A striking increase in urine zinc levels occurs in post-operative procedures, major long bone fractures, burns, chronic malabsorption states and patients on long-term TPN. The excessive urinary loss of zinc following these kinds of stresses must be replaced in order to insure proper nutritional rehabilitation of the patients. Zinc is also lost through sweat, in hair and sloughing skin.

The first syndrome of zinc deficiency in adult human beings on TPN was reported in 1975. Four patients with severe gastrointestinal disorders who underwent zinc-free TPN therapy developed paranasal, perioral and periorbital dermatitis, diarrhea, alopecia and mental depression. Plasma zinc concentrations ranged from 9 to 12 μg/100 mL. Urinary zinc was high with values as high as 23,600 μg/day. Intravenous or oral administration of zinc sulfate in doses of 40 to 200 mg daily, rapidly reversed skin lesions, diarrhea and mental depression. The alopecia was resolved more slowly.

Numerous reports of all or some of the zinc deficiency symptoms in adults, children and premature infants then followed. The most predominant clinical manifestations of zinc deficiency in TPN reported were the skin lesions and diarrhea which resembled that found in acrodermatitis enteropathica.

Plasma zinc levels also declined in premature infants maintained on TPN without supplementation. During the last 10 to 12 weeks of pregnancy, two-thirds of the infant's zinc stores are transferred from the mother. This patient population is at high risk of developing zinc deficiency because they are born with low body stores, need zinc for growth and may be in negative zinc balance up to 60 days after birth.

Therefore, providing zinc during TPN prevents development of the following deficiency symptoms: parakeratosis, hypogensia, anorexia, dysosmia, geophagia, hypogonadism, growth retardation and hepatosplenomegaly.

Copper

Copper plays a key role as a component of numerous metalloenzymes and proteins such as: cytochrome oxidase, ferroxidases, amine oxidases, superoxide dismutase, ceruloplasmin and metallothioneine. Specific biological functions for which copper is responsible are hemoglobin synthesis, growth and development, pigmentation, fertility and reproduction, coordination and nerve function, protection against oxygen radicals, connective tissue maturation, cardiovascular integrity, bone formation and

immunocompetence. The highest concentrations of copper content in the human body are in the liver, brain and heart.

Absorption of copper occurs predominantly in the stomach and upper small intestine. The exact mechanism of copper absorption from the gastrointestinal tract into the blood is elusive. Normal serum copper values range from 80 to 163 μg/dL (mean, approximately 110 μg/dL). A report stated that copper concentrations are higher in serum than in plasma. After absorption, copper exists loosely bound to albumin in the plasma for transport and exchange with tissues. In circulation toward the liver, copper may be stored or combined with ceruloplasmin or erythrocuprein. The α_2-globulin, ceruloplasmin, harbours greater than 90% of serum copper. More than 60% of the copper in erythrocytes is associated with erythrocuprein. The daily turnover of copper through ceruloplasmin is approximately 0.5 mg. Diet, age, hormones and pregnancy influence the concentration of copper in the liver.

The liver is responsible for the excretion of copper, primarily bile (80%). Eighteen and 4% of the trace element is eliminated through the intestinal wall and in the urine, respectively. Biliary copper is known to form a complex with the bile salt taurochenodeozylate and bilirubin. Small amounts of copper are also lost through menstruation and in sweat. Copper losses in the urine of normal subjects amounted to 0.01 to 0.06 mg/day.

Human copper deficiency was first documented in 1964. Infants who were recovering from marasmus or milk diets with no food sources, exhibited deficiency manifestations such as anemia, decreased plasma copper and ceruloplasmin levels, intermittent neutropenia, severe osteoporosis and pathological fractures.

This deficiency syndrome with laboratory and clinical manifestations, has now been recognized in adults and children who were receiving parenteral nutrition without copper supplementation. A consistent decline in plasma copper content can be seen without copper supplementation.

Providing copper during TPN helps prevent development of the following deficiency symptoms: leukopenia, neutropenia, anemia, depressed ceruloplasmin levels, impaired transferrin formation and secondary iron deficiency.

Manganese

Manganese is an essential nutrient that serves as an activator for enzymes such as polysaccharide polymerase, liver arginase, cholinesterase and pyruvate carboxylase.

Manganese is bound to a specific transport protein, transmanganin, a β-l-globulin. Manganese is widely distributed but concentrates in mitochondria-rich tissues such as brain, kidney, pancreas and liver. The concentration in skeletal muscle is very low. Manganese is also found in bone but cannot be mobilized to meet body needs. Newborns do not have a special store. Assays for manganese in whole blood result in concentrations ranging from 6 to 12 μg per liter.

Excretion of manganese occurs mainly through the bile. The liver appears to maintain manganese homeostasis. In the event of obstruction and overload, ancillary excretion routes include pancreatic juice or crossing the intestinal lumen of the duodenum, jejunum or ileum. Urinary excretion is negligible.

Providing manganese during TPN helps to maintain manganese serum levels and to prevent depletion of endogenous stores. Administration of manganese helps prevent deficiency symptoms such as nausea and vomiting, weight loss, dermatitis and changes in growth and colour of hair.

Besides animal experiment results, there exists one human case of manganese deficiency. A volunteer patient was observed for Vitamin K deficiency under metabolic ward conditions. Weight loss, transient dermatitis, occasional nausea and vomiting, hair and beard colour change, and slow growth of hair and beard were noted and recorded. Protein synthesis was not affected. Remarkably, hypercholesterolemia was evident. It was later discovered that the addition of manganese to the purified mixture was overlooked.

Chromium

Trivalent chromium is part of glucose tolerance factor (GTF), an essential activator of insulin-mediated reactions. Chromium helps to maintain normal glucose metabolism and peripheral nerve function. Its mode of action is described as facilitating the reaction of insulin by fine tuning the receptor sites of sensitive tissues.

Serum chromium is bound to transferrin (siderophilin) in the β-globulin fraction. Typical blood levels range from 1 to 5 μg per liter, but blood levels are not considered a meaningful index of tissue stores.

Administration of chromium supplements to chromium deficient patients can result in normalization of the glucose tolerance curve from the diabetic-like curve typical of chromium deficiency. This response is viewed as a more meaningful indicator of chromium nutriture than serum chromium levels.

Excretion of chromium is via the kidneys, ranging from 3 to 50 μg/day. Several researchers reported urinary chromium loss in subjects not receiving TPN to be within the range of <1.0 to 7.0 μg per liter, with an average output of <5 μg/24 hours. In contrast, those patients receiving TPN excreted much higher amounts of chromium, within a range of 10 to greater than 100 μg of chromium per day.

Biliary excretion via the small intestine may be an ancillary route but it is believed that only small amounts of chromium are excreted in this manner. When insulin-requiring diabetics are given Cr-labeled chromic chloride intravenously, an increase in urinary excretion is observed when compared to normal subjects.

Providing chromium during TPN helps prevent deficiency symptoms which include impaired glucose tolerance, ataxia, peripheral neuropathy and a confusional state similar to mild/moderate hepatic encepholopathy.

INDICATIONS

M.T.E. -4 is indicated for use as a supplement to intravenous solutions given for TPN. Its administration in TPN solutions helps to maintain plasma zinc, copper, manganese, and chromium levels, and to prevent depletion of endogenous stores of these trace elements and subsequent deficiency symptoms.

CONTRAINDICATIONS

M.T.E.-4 and M.T.E.-4 CONCENTRATED (Multiple Doses) are not for use in newborns. Benzyl alcohol, a preservative in this product, has been associated with toxicity of newborns. Data is unavailable on the toxicity of other preservatives in this age group.

WARNINGS

M.T.E.-4 is a hypotonic solution which should be administered in admixtures only.

If toxicity symptoms occur due to any one of the trace elements in M.T.E.-4, discontinue supplementation of TPN solutions immediately.

Do NOT give undiluted M.T.E.-4 by direct injection into a peripheral vein because of the potential of infusion phlebitis.

PRECAUTIONS

The possibility of zinc retention should be a consideration in patients with renal dysfunction and caution should be exercised since zinc is excreted via the kidneys.

The possibility of copper and manganese retention is a consideration in patients with biliary obstruction since both of these trace elements are eliminated via the bile.

In diabetic patients, the contribution of chromium supplementation for maintenance of normal glucose homeostasis has to be taken into account. In all diabetic patients, the hyperglycemia should also be controlled with appropriate therapy.

ADVERSE REACTIONS

No adverse reactions have been reported for the amounts of zinc, copper, manganese and chromium in the M.T.E.-4. The amounts of these trace elements are small and toxicity symptoms are not likely to occur at the suggested dosage level.

OVERDOSAGE

Zinc

Zinc is a relatively non-toxic compound but toxicity can occur by oral administration, inhalation and hemodialysis. Ingestion of excess zinc has usually resulted from storage of food or beverages in galvanized containers, which results in diarrhea, vomiting and fever. One report of intoxication following inhalation of zinc oxide fumes causing fever, headache and vomiting has been reported in the literature. In 1972, a case of zinc poisoning was reported in a patient on hemodialysis with zinc-contaminated water. The patient developed nausea, vomiting, fever and severe anemia.

Infusion of 40 to 80 mg/day of zinc have been used with no apparent ill effects. No adverse effects were reported when a group of 22 patients received a 20 mg infusion before and after surgery. One case of ill effects was reported when a daily 10 mg dose of zinc was infused over one hour for 5 days. The ill effects were tachycardia, hypothermia, profuse sweating and blurred vision.

One death resulted from an overdose of intravenous zinc which was due to a local prescribing error. A 72 year old woman with a high output enterocutaneous fistula inadvertently received a 1683 mg (7.4 g) dose of zinc infused over a 60-hour period. Analysis of her serum zinc showed a zinc level of 4184 μg/100 mL. Clinical manifestations were edema, jaundice, vomiting, diarrhea and oliguria.

Seven patient who received an accidental overdosage (25 mg zinc/liter TPN solution; equivalent to 50 to 70 mg zinc/day) exhibited hyperamylasemia (557 to 1850 Klein Units; normal 130 to 310).

Copper

Symptoms of copper toxicity reported include prostration, behaviour change, diarrhea, progressive marasmus, hypotonia, photophobia and peripheral edema. D-penacillamine has been reported effective as an antidote.

Manganese

There have been no manganese toxicity reports in the literature of patients on TPN or from oral intake.

Chromium

Chromium toxicity symptoms include nausea, vomiting, ulcers of the gastrointestinal tract, renal and hepatic damage, convulsions and coma. A woman who received only 5.3 μg of chromium daily in her TPN solution for years as a protein hydrosylate contaminant began to exhibit signs of chromium deficiency. As treatment she received 250 μg/day for two consecutive weeks without toxic effects.

DOSAGE AND ADMINISTRATION

DOSAGE

The suggested dosage ranges for the 4 trace elements are:

ZINC

Adults: For the metabolically stable adult receiving TPN, the suggested intravenous dosage level is 2.5 to 4 mg of zinc per day.

For acute catabolic states an additional 2 mg of zinc per day is suggested.

For the stable adult with fluid loss from the small bowel, an additional 12.2 mg of zinc per liter of TPN solution; or an additional 17.1 mg of zinc per kg of stool or ileostomy output is recommended.

Pediatrics: For full-term infants and children up to 5 years of age, 100 µg zinc/kg/day is recommended.

For premature infants weighing up to 3 kg in body weight, 300 µg zinc/kg/day is recommended.

COPPER

Adults: For the metabolically stable adult receiving TPN, the suggested additive dosage level is 0.5 to 1.5 mg copper per day.

Pediatrics: For pediatric patients the suggested dosage level is 20 µg copper per kg daily.

MANGANESE

Adults: For the metabolically stable adult receiving TPN, 0.15 to 0.8 mg/day is suggested as the additive dosage level for manganese.

Pediatrics: A dosage level of 2 to 10 µg of manganese per kg daily is recommended.

CHROMIUM

Adults: For the metabolically stable adult receiving TPN, 10 to 15 μg of chromium per day is suggested as the additive dosage level.

The metabolically stable adult with intestinal fluid loss may require 20 μg of chromium daily with frequent monitoring of blood levels as a guideline for subsequent administration.

Pediatrics: For pediatric patients, 0.14 to 0.20 μg/kg/day is suggested as the additive dosage level.

ADMINISTRATION

Periodic monitoring of zinc, copper, manganese and chromium plasma levels is suggested as a guideline for administration.

Normal plasma levels for zinc vary from approximately 88 to 112 μg per 100 mL. Frequently monitor the blood zinc levels for those patients receiving more than the usual maintenance dosage level of zinc.

The normal plasma range for copper is approximately 80 to 160 μg per 100 mL.

M.T.E.-4 should be aseptically added to the TPN solution under the laminar flow hood. The trace elements present in M.T.E.-4 are physically compatible with electrolytes and vitamins usually present in the amino acid/dextrose solution used for TPN.

Visually inspect parenteral drug products for particulate matter and discolouration prior to administration whenever container and solution permit.

PHARMACEUTICAL INFORMATION

Trade Names: M.T.E.-4 and M.T.E.-4 Concentrated

Proper Names: Multi-Trace Element-4 and Multi-Trace Element-4 Concentrated

Chemical Name	Molecular Formula	Molecular Weight
Zinc Sulfate, Heptahydrate	$ZnS0_4.7H_20$	287.54
Copper Sulfate, Pentahydrate	$CuS0_4.5H_20$	249.68
Manganese Sulfate, Monohydrate	$MnS0_4.H_20$	169.01
Chromic Chloride, Hexahydrate	$CrCl_3.6H_20$	266.45

Description: M.T.E.-4 is a sterile, non-pyrogenic solution of four trace elements for use as an additive for Total Parenteral Nutrition (TPN). Zinc Sulfate is chemically designated $ZnS0_4$, a white crystalline compound freely soluble in water. Cupric Sulfate is chemically designated $CuS0_4$, a blue crystalline compound very soluble in water. Manganese Sulfate is chemically designated $MnS0_4$, a pale red compound soluble in water. Chromic Chloride is chemically designated $CrCl_3$, a greenish compound soluble in water. The pH (approximately 2.0) is adjusted with sulfuric acid and/or sodium hydroxide.

Composition: Each mL contains:

Ingredients	M.T.E-4			M.T.E.-4 Concentrated	
	Single Dose Vials		Multiple Dose Vial	Single Dose Vial	Multiple Dose Vial
	3 mL Fill	10 mL Fill	30 mL Fill	1 mL Fill	10 mL Fill
Zinc (as Zinc Sulfate heptahydrate)	1.0 mg	1.0 mg	1.0 mg	5.0 mg	5.0 mg
Copper (as Cupric Sulfate pentahydrate)	0.4 mg	0.4 mg	0.4 mg	1.0 mg	1.0 mg
Manganese (as Manganese Sulfate monohydrate)	0.1 mg	0.1 mg	0.1 mg	0.5 mg	0.5 mg
Chromium (as Chromic Chloride hexahydrate)	4.0 µg	4.0 µg	4.0 µg	10.0 µg	10.0 µg
Benzyl Alcohol NF	-	-	0.9%	-	0.9%
Water for Injection USP	q.s.	q.s.	q.s.	q.s.	q.s.

Dilution for Intravenous Use:
Aseptic addition of M.T.E. -4 to the TPN solution under a laminar flow hood is recommended. The trace elements in M.T.E.-4 are physically compatible with the electrolytes and vitamins usually present in the amino acid/dextrose solution used for TPN. Inspect for particulate matter and discolouration prior to administration whenever solution and container permit.

STABILITY OF SOLUTIONS

Storage

Store between 15 and 30°C (59 and 86°F). Do not permit to freeze.

AVAILABILITY OF DOSAGE FORMS

M.T.E. -4 is supplied in boxes of 25 as 3 mL and 10 mL single-dose, flip-top vials and 30 mL, multiple-dose, flip-top vials.

Each mL provides: Zinc 1.0 mg, Copper 0.4 mg, Manganese 0.1 mg, and Chromium 4.0 μg.

M.T.E.-4 Concentrated is supplied in boxes of 25 as 1 mL, single-dose, flip-top vials and 10 mL, multiple-dose, flip-top vials.

Each mL provides: Zinc 5.0 mg, Copper 1.0 mg, Manganese 0.5 mg, and Chromium 10 μg.

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* Hard copies of literature available on request.