PRODUCT MONOGRAPH

MICRO Cu

Cupric Sulfate Injection USP

(CU^{2+} 0.4 mg/mL and 2.0 mg/mL)

Trace Element

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CLINICAL PHARMACOLOGY

Copper is an essential nutritional element that is important in many enzyme systems either as a metalloenzyme or an enzyme activator such as: cytochrome-c-oxidase, dopamine-B-hydroxylase, monamine oxidase, superoxide dismutase, tyrosinase, urate oxidase, ceruloplasmin, ferroxidases and metallothionine.

The clinical importance of copper is related to the development and maintenance of collagen protein cross-linkage, structure and function of the central nervous system, iron metabolism, erythropoiesis and pigmentation.

In man, the highest concentrations of copper are found in the liver and brain. Copper is absorbed primarily from the stomach and jejunum however the exact mechanism of absorption is not clear.

Normal serum plasma levels range from 90 to 130 μg/100 mL (mean, approximately 110 μg/100 mL).

Absorbed copper is loosely bound to serum albumin and amino acids for transport and exchange with tissues. After reaching the liver, copper is either stored or released for incorporation into erythrocuprein, ceruloplasmin and the numerous copper containing enzymes.

About 60% of the copper in red blood cells is associated with erythrocuprein while the remainder is more loosely bound to protein. Copper in plasma is present in two main forms of which 90% is firmly bound to ceruloplasmin and a small percentage is loosely bound to albumin. The remainder is bound to amino acids and enzymes.

Age, diet, hormones and pregnancy influence liver and plasma concentrations of copper.

Copper is excreted primarily via the bile (approximately 80%) in the form of a nonabsorbable protein complex with a further 18% via the intestinal wall and 2 - 3 % via urine. Consequently, ingestion of 2 - 5 mg of copper per day, would result in copper losses of 0.6 to 2 mg per day, with 0.01 to 0.06 mg in urine. Comparatively small amounts are lost through menstruation and in sweat.

Copper deficiency has been recognized in infants on cow's milk diets and in malnourished infants being rehabilitated on high-calorie low copper diets. Symptoms experienced include anemia, hypoproteinemia, low serum copper and iron levels, neutropenia, diarrhea and "scurvy-like" bone changes.

Adults and children receiving total parenteral nutrition (TPN) without copper supplementation have shown these same indications along with a parallel decline in plasma copper.

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

INDICATIONS

Micro Cu (Cupric Sulfate Injection USP) is indicated for use as a supplement to intravenous solutions given for TPN. Its administration in TPN solutions helps to maintain plasma copper levels and to prevent depletion of endogenous stores of copper and subsequent deficiency symptoms.

WARNINGS

Micro Cu is a hypotonic solution which should be administered in admixtures only.

If toxicity symptoms occur due to copper, discontinue supplementation of TPN solutions immediately.

Do not give undiluted **Micro Cu** by direct injection into a peripheral vein because of the

potential of infusion phlebitis.

PRECAUTIONS

The possibility of copper retention should be a consideration in patients with biliary obstruction and caution should be exercised since copper is eliminated via the bile.

ADVERSE REACTIONS

No adverse reactions have been reported for the amount of copper present in this product. The amount is small and toxicity symptoms are not likely to occur at the suggested dosage level.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Ingestion of excess copper due to the storage of food or beverages in copper or brass vessels, and beverage vending machines has resulted in acute gastrointestinal illness. Adverse reaction experienced following the ingestion of large doses of copper sulfate (1 to 50 g) include nausea, vomiting, metallic taste, burning sensation in the oesophagus and stomach, colic, bloody diarrhea, convulsions, hypotension and coma, renal damage with acute kidney necrosis, jaundice associated with liver injury and haemolysis, anuria/oliguria, hemolytic anemia.

Symptoms of copper toxicity that have been reported include prostration, behaviour change, diarrhea, progressive marasmus, hypotonia, photophobia and peripheral edema. D-

penacillamine has been reported effective as an antidote.

DOSAGE AND ADMINISTRATION

DOSAGE

The suggested dosage ranges are:

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.

ADMINISTRATION

Routine monitoring of copper plasma levels is suggested as a guideline for administration. The normal plasma range for copper is approximately 90 to 130 μg per 100 mL.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Cupric sulfate

Chemical Name: Copper sulfate pentahydrate

Molecular Formula: $CuSO_4 \cdot 5H_2O$

Molecular Weight: 249.68

Description: Copper sulfate occurs as a blue crystal or powder. It effloresces slowly in dry air. Its solution is acid to litmus. It is freely soluble in water and in glycerin, very soluble in boiling water and slightly soluble in alcohol.

COMPOSITION

Micro Cu contains copper sulfate pentahydrate in water for injection, with sulfuric acid for pH adjustment.

STABILITY AND STORAGE RECOMMENDATIONS

Store at controlled room temperature not exceeding 28°C. Do not permit to freeze.

DILUTION FOR INTRAVENOUS USE

Aseptic addition of **Micro Cu** to the amino acid/dextrose component of a TPN solution under a laminar flow hood is recommended. After dilution, the solution must be used within 24 hours.

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

AVAILABILITY

Two strengths, 0.4 mg copper/mL and 2 mg copper/mL (concentrate), are available in single dose 10 mL clear glass vials in boxes of 10.

Micro Cu is for intravenous use after dilution only.

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