Chapter 12

MANGANESE

Noel W. Solomons, M.D.

I. Product Information

A. Introduction

Manganese is found ubiquitously in mammalian organisms, and at least two metalloenzymes of manganese — Mn-superoxide dismutase and pyruvate carboxylase — have been identified. In addition, the divalent ion of manganese is believed to play a role as a soluble co-factor, analogous to that of magnesium, in several intracellular reactions. The most notable projected role for soluble manganese is in the linking of the carbohydrate moities to mucopolysaccharides in the formation of connective tissue structures of a cartilaginous nature.[1] Manganese deficiency syndromes are well known in livestock, especially fowl. Gestational manganese deficiency in animals — both experimental and acquired — produces severe

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teratogenesis in offspring.[2] However, evidence for the occurrence of overt manganese deficiency in human subjects is largely lacking. A putative case of manganese deficiency in a young man has been published,[3] but generalizations from this case to other clinical situations have been troublesome. As such, no case of TPN-induced manganese deficiency has been seen. TPN, however, is associated with negative manganese balance when solutions are not supplemented with this mineral and the AMA expert committee[4] saw fit to establish a parenteral requirement for manganese for individuals undergoing TPN.

B. Chemistry

Manganese has an atomic number 26, and an atomic weight of 54.938. It exists in a wide variety of valence states, the most common being 2, 4 and 7. In the common, inorganic salts (i.e. sulfate, chloride), manganese is in the divalent, Mn(II) form, and both salts are exquisitely soluble in cold water. The divalent form is stable in aqueous solution.

C. Dosage Forms/Concentrations/Manufacturers

The AMA[4] has recommended that the trace element solution contain an ionic concentration of 0.1 mg/ml. The preferred salt for intravenous use was specified as manganese sulfate ($MnSO_4 \cdot H_2O$, mol wt 169), which contains 32.5% Mn(II). Thus, the salt concentration would be 0.308 mg/ml (see Table I).

D. Uses/Functions

Unlike the other trace minerals discussed in this section, overt clinical deficiency of manganese in a patient undergoing TPN has not been recognized. Manganese, however, was among the trace minerals considered indispensable for adequate nutritional maintenance during TPN.[4] It is thus recommended as routine in both pediatric and adult regimens alike. Since there is mounting evidence that intracellular, ionic Mn(II) plays a preferential co-factor role in certain hepatic enzymes in energy metabolism,[5] it is possible that increased efficiency of energy utilization might be achieved by maintenance of normal manganese stores during TPN. Animal studies have demonstrated a profound teratogenic effect of maternal manganese deprivation.[6] The theoretical possibility that this could result in a human pregnancy in which the mother was deprived of manganese intake is reasonable. As TPN is now applied even in pregnancy, avoidance of such a potential adverse consequence merits rigorous attention to manganese delivery to pregnant women undergoing TPN.

TABLE I. Commercially Available Manganese Products

Product	Manufacturer	Type of Salt	Ionic Conc. (mg/ml)	Container
Manganese Chloride	Abbott	Chloride	0.1	10, 50 ml vials
Manga Trace™	Armour	Chloride	0.1	10 ml vials
Manganese Sulfate, USP	LyphoMed	Sulfate	0.1	10 ml vials
Manganese Sulfate, USP	LyphoMed	Sulfate	0.1	30 ml MDV
Manganese Sulfate, USP	LyphoMed	Sulfate	0.5	10 ml vials (concentrate)

II. Professional Implications

A. Preparation/Compounding/Analysis/Synthesis

Ultrapure forms of manganese salts are available for the preparation of additive solutions. Neutron activation analysis probably provides a more precise and accurate determination of manganese concentration in additives and TPN fluids than atomic absorption spectrophotometry, but adequate measurements can be made using AAS.

B. Antagonists/Inhibitors/Potentiators/Synergistic Agents

None known.

C. Contraindications/Precautions/Warnings

Since manganese is excreted in the bile, the administration of parenteral manganese to patients with cholestatic conditions might be contraindicated.

D. Pharmacokinetics/Disposition

1. Bioavailability/Absorption

Data on the bioavailability of dietary or parenteral manganese is scarce. Few factors pertaining either to the host or to TPN therapy itself would suggest avenues for reduced or enhanced utilization of parenterally-

administered manganese.

2. Distribution/Binding

The total-body content of manganese in an adult is estimated to be 20 mg. It is concentrated in the liver and in other mitochondrion-rich tissues. In the blood, it is found both in the red cell, associated with hemoglobin,[7] and in the serum, associated with a beta-1-globulin.[8]

3. Blood Levels

Currently, the best estimates for normal plasma manganese levels range from 0.38 to 1.04 ug/L (mean 0.57 ug/L).[9]

4. Metabolism

It is clear that manganese is a component of metalloproteins. It is also thought to serve as a soluble, ionic co-factor in certain pathways in intermediary energy metabolism. Recent evidence suggests that manganese in liver cells interchanges between a bound and a free state after a meal,[5] adding legitimacy to the potential for a co-factor function.

5. Excretion

Manganese is largely excreted from the body into the fecal stream in bile, and to a lesser extent in intestinal secretions. Renal excretion of manganese is minimal.

III. Patient Considerations

A. Administration

Parenteral manganese is administered by diluting the appropriate individual dose from a commercial additive preparation into a TPN infusate. It can be added from a single-entity preparation, or as part of a multielement preparation subject to the considerations for the use of multiple-mineral additives (discussed previously in this section). Of all of the minerals in the conventional multi-element additives, manganese is the least likely to require an alteration of dosage.

B. Adverse Reactions

None known.

C. Monitoring

Monitoring manganese status presents multiple problems. Functional changes with subclinical deficiency or early toxicity are not well described.

The determination of manganese concentrations in biological materials is not as well developed as that for zinc and copper; the most precise and accurate analytical methodology is probably neutron activation, a technique with limited accessibility in most hospitals. The relationship of circulating manganese to total-body stores is poorly developed, and plasma, serum, red cell or whole blood manganese concentration cannot be used clinically to monitor nutritional status; whole blood manganese levels do rise in individuals chronically exposed to the mineral,[10] suggesting that iatrogenic manganese overload might be amenable to detection by measuring this index. Determination of the manganese-dependent mitochondrial superoxide dismutase has a potential role in assessing human manganese nutriture,[11] but selecting an appropriate, accessible tissue biopsy source from man poses a problem at the moment.

D. Expiration

The expiration date on the commercially available product will provide the expected shelf-life of manganese trace element. Single use vials should be discarded within 24 hours in spite of the preservative action of certain trace elements. TPN solutions containing manganese trace elements may be stable for up to 24 hours unless otherwise determined. It should be remembered that Maillard reaction products have been shown to chelate trace elements.[12]

E. Storage

Most trace mineral additives do not contain bacteriostatic agents. They must be discarded after a single use.

F. Requirements/Deficiencies

As noted, a clinical deficiency syndrome of manganese associated with TPN has not been reported. In fact, only one, somewhat dubious case report of human manganese deficiency has been reported.[3] It occurred in an experimental subject on a formula diet, and the manifestations revolved around changes in hair growth and pigmentation, general well-being, and hypocholesterolemia, all of which responded to the administration of manganese. The concentration of manganese in TPN solutions is usually low. Since a deficiency or depletion state with respect to manganese cannot be readily identified on clinical or laboratory bases, only maintenance level amounts of manganese (0.15 to 0.8 mg), adjusted downward for patients with biliary disease, will be required. In pregnancy, however, the theoretical possibility of fetal malformation obligates at least a maintenance dosage of manganese, and at the discretion of the physician, perhaps an increment.

G. Dose (Treatment/Toxicity)

The recommendation for daily parenteral requirements comes from the AMA panel[4] (see Appendix A. General Tables). For children it is 2 to 10 ug/kg of body weight, equivalent to 20 to 100 ug daily for a 10.5 kg one-year-old. For stable adults, the daily parenteral requirement has been estimated at 0.15 to 0.8 mg, assuming a dietary requirement of 0.7 to 2.5 mg and an absorption factor of 50%. This was further adjusted for the presumed lesser fecal excretion of the mineral in the bowel at rest. Excessive industrial exposure to manganese in mine workers produces neurological sequelae, but no similar consequences are known with dietary manganese, and thus are not to be expected from parenteral administration of maintenance doses in the absense of a severe excretory defect.

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