PARENTERAL TRACE ELEMENTS: IRON*

JAMES D. COOK M.D.
Division of Hematology
University of Kansas Medical Center
Kansas City, Kansas

IT is doubtful whether any form of life exists in the absence of iron. As the functional core of the heme proteins myoglobin and hemoglobin, iron plays a critical role in oxygen storage and transport. Other heme proteins, such as the cytochromes, take part in electron transport reactions in mitochondria and endoplasmic reticulum. Iron is also a part of the so-called "iron sulfur" proteins or nonheme enzymes, including such compounds as succinate dehydrogenase, NADH dehydrogenase, and xanthine oxidase. So important is this metal in man that highly specialized proteins have been developed for efficient extracellular transport (transferrin) and intracellular storage (ferritin).

EVIDENCE FOR HUMAN REQUIREMENTS

Body iron resides in two major compartments: *functional iron,* which consists mainly of hemoglobin and myoglobin, and *storage iron,* which serves to replace any losses from the functional compartment. A constant supply of iron is required by the erythroid marrow for hemoglobin production in developing red cells. Once iron stores have been depleted, a continuing decline in body iron is associated with a progressive fall in circulating hemoglobin which may become life-threatening.

During recent years various nonhematologic consequences of iron deficiency have received increasing attention.[1] Animal studies have shown that iron deficiency without anemia is associated with severe muscle dysfunction, apparently explained by a reduced concentration of alpha-glycerophosphate oxidase,[2] an enzyme concerned with electron transport by the mitochondrial membrane. A spectrum of abnormalities, especially in epithelial tissues, are associated with iron deficiency, which accounts

*Presented as part of the *Working Conference on Parenteral Trace Elements-II* held by the Section on Clinical Nutrition of the New York Academy of Medicine and the Department of Foods and Nutrition of the American Medical Association at the Academy September 14 and 15, 1982.

Supported by USAID Cooperative Agreement DAN-0227-A-00-2104-00.

RECOMMENDED DAILY INTAKE OF IRON*

	AGE (years)	*IRON* (mg/day)
Infants	0.5-3	15
Children	4-10	10
Male	11-18	10
Female	11-18	18
Men	>18	18
Women	19-50	18
	>50	10

*Based on U.S. RDA (1974).

for the angular stomatitis, esophageal webbing, chronic gastritis, and gastric atrophy observed in long-standing iron deficiency. There is some evidence that iron deficient children develop abnormalities in brain function manifested by irritability, impaired concentration, and behavioral changes.[3,4] Tissue iron deficiency reduces resistance to infection by impairing lymphocyte transformation,[5] reducing the percentage of circulating T-cells,[6] and impairing phagocytic killing of bacteria by reducing myeloperoxidase in circulating granulocytes.[7] Recent animal studies indicate that iron is required in the maintenance of normal body temperatures.[8]

Quantitative Requirement in Normal Individuals by the Oral Route

Dietary iron requirements. The recommended daily intakes of iron for age and sex are listed in the table. It should be noted that these recommendations are based on debatable assumptions about dietary iron availability. The recommended iron intake for infants is relatively high because of their smaller body size and continued growth requirements. Iron requirements vary markedly during the first year of life; the newborn infant begins with a generous endowment of storage iron from the mother, but this becomes exhausted because of growth by about four months of age. The recommended intake for full-term infants is 1 mg/kg body weight/day, to a maximum of 15 mg starting no later than four months and continuing until three years of age.[9] The recommendation for low birth weight infants is 2 mg/kg/day, starting no later than two months of age.

For adults the recommended iron intake in women is nearly twice that of men, primarily because of menstrual blood loss. Because the nature of the diet has a significant effect on iron availability, recommendations by the FAO and WHO are based on the proportion of calories derived from

animal foods.[10] It is generally accepted that the total intake of dietary iron is less important than the availability of this iron. The dietary content of animal tissue and ascorbic acid are the main determinants of iron availability. The presence of meat is particularly important and in fact is the main dietary factor known to correlate with iron status in populations studies.[11]

Efficiency. Food iron is absorbed from two separate pools: heme and nonheme iron.[12] The absorption of *nonheme* iron, which comprises about 90% of dietary iron, varies markedly with iron status and with the nature of the meal. Because of the lower iron requirement of adult men (about 1 mg/day), an absorption of only 5% of nonheme iron is adequate to maintain iron balance. With severe iron deficiency, the ceiling absorption of nonheme iron is about 20%. Absorption of *heme* iron, which enters the mucosal cell as an intact porphyrin complex, averages 30 to 40%. Assimilation of heme iron is largely unaffected by the nature of the diet and varies less with body iron stores than does nonheme iron. Absorption studies indicate that with a Western diet containing about 10% heme iron, the latter accounts for about one third and nonheme for about two thirds of the iron absorbed each day.[13]

A clear distinction must be made between absorption of dietary iron and of medicinal iron. The intake of food iron is small in comparison to the large amounts that can be administered therapeutically. A maximum of about 3 mg iron can be absorbed from a normal diet as compared to 20 to 30 mg daily with conventional doses of ferrous sulfate.

Excretory routes. One of the fundamental features of iron metabolism is that no mechanism exists to excrete excessive amounts of the metal. Body iron stores act as a buffer to sequester iron in excess of bone marrow requirements for hemoglobin production. Modest increases in body iron are confined to reticuloendothelial cells wherein the metal seems to be relatively innocuous. A continued increase in body iron ultimately leads to parenchymal iron overload and cellular damage in organs such as the liver, heart, pancreas, and pituitary.

Although there is no excretory mechanism for iron, obligatory losses occur from the skin, gastrointestinal tract, and genitourinary tract.[14] In normal adult men, basal loss is 12 to 14 ug/kg/day. About one third of this is due to red cell extravasation in the gastrointestinal tract and two thirds from exfoliation of epithelial cells in the skin and the gastrointestinal tract. Although body iron cannot be regulated by alteration in iron loss by these pathways, obligatory losses vary to some extent with iron status. In the severely iron deficient patient, obligatory losses may fall to 8 ug/kg/day

and increase to perhaps 20 ug/kg/day in patients with iron overload.

Absolute requirements. A normal adult man has an obligatory iron requirement of about 1 mg iron/day. Women, infants, and children have additional needs due to physiological requirements of growth, menstruation, and pregnancy. The average iron requirement in boys and girls is about 0.5 mg/day. In boys this requirement reaches a peak of about 1 mg in the late teens, whereas teenage girls require 1.5 mg iron/day because of menstrual losses. The latter average about 28 ml blood or 12 mg iron monthly in adult women,[15] but the distribution of menstrual loss is highly skewed, and about 10% of women have losses in excess of 80 ml blood/month or 1 mg iron daily.[16] The iron requirement for a normal pregnancy is 400 to 500 mg.[17] There is an additional iron requirement during lactation although this is partially offset by the absence of menstrual loss. The iron concentration of human breast milk is low—about 1 mg/L in the first month postpartum and about 0.3 mg/L between four and six months.[18]

In addition to these physiologic losses, additional iron demands may be overlooked clinically. Regular blood donations may go unmentioned, although an adult man with normal iron stores of 1,000 mg can donate about four units per year before exhausting his iron reserve if he were to absorb nothing from the gastrointestinal tract. Chronic aspirin ingestion is often associated with an increase in gastrointestinal blood loss because of gastric inflammation and impaired platelet function.

Toxicity, range of safe and adequate intake. The risk of iron toxicity depends on the type of iron and whether it is given orally or parenterally. Even small amounts of inorganic iron may be highly toxic when administered intravenously, a fact that precludes programs of daily intravenous administration of iron in this form. In normal individuals a maximum of 220 to 300 ug iron/100ml plasma can be firmly bound by unsaturated transferrin or a total dose of 5 to 10 mg. Unbound iron administered intravenously in excess of the binding capacity produces flushing, headache, tachycardia, and eventually circulatory collapse. Parenteral iron must therefore be administered as a firmly bound complex such as iron dextran (Imferon) or iron sorbitol (Jectofer). Iron can also be administered as repeated blood transfusions but this is associated with other risks such as transfusion reaction or circulatory overload. Continued administration of excess parenteral iron in any form will ultimately lead to body iron overload and associated parenchymal cell damage. On a long-term basis the only quantity of iron that can be considered entirely safe is that which

exactly balances iron loss.

Toxicity from oral iron administration is less precisely defined. Conventional doses of oral iron (60 mg ferrous sulfate tid) are associated with significant gastrointestinal side effects in 10 to 20% of patients. Whereas the frequency of lower gastrointestinal tract side effects such as constipation and diarrhea is not dose-dependent, such upper gastrointestinal symptoms as nausea and epigastric distress increase progressively at higher doses, and place a ceiling on the amount of iron that can be administered orally. Acute iron poisoning was a relatively common cause of death in children before desferrioxamine became available for treatment. Death from acute iron poisoning is due to extensive erosion of the intestinal mucosa and massive influx of inorganic iron to the circulation.

Toxicity from excessive intake of dietary iron has been recorded only in the South African Bantu.[12] However, recent studies have confirmed the genetic nature of idiopathic hemochromatosis, and have shown that heterozygotes may make up a large segment of an ostensibly normal population.[19] An inherited defect in the regulatory mechanism for iron absorption might explain the occurrence of severe iron overload in an occasional patient taking normal quantities of therapeutic iron over several years.

In the past, moderate amounts of parenteral iron have been considered relatively safe but recent studies argue otherwise. In patients undergoing chronic hemodialysis it has been common practice to administer parenteral iron, usually Imferon, at regular intervals to replace blood losses from laboratory sampling and the dialyzing procedure. It has been reported recently that these patients may develop organ damage due to progressive iron accumulation.[20]

Altered Requirements in Disease States

An enhanced requirement for iron in various disease states is almost invariably due to increased blood loss, although a rare patient with nephrotic syndrome may lose large amounts of transferrin-bound iron in his urine. A variety of disease states such as malignancy and inflammation may reduce the efficiency of gastrointestinal absorption of iron. There are innumerable sources of blood loss clinically, but often the most important one in the hospitalized patient is the clinical laboratory.

Requirements by the Intravenous Route

There is little or no need for daily administration of intravenous iron. If

iron intake were to cease in an adult man with normal losses, it would be three to four years before he would develop iron deficiency anemia. Even in a hospitalized patient with high iron requirements due to continued blood loss, iron demands should be met by oral administration. If this is not possible, parenteral iron is required. It is common practice to administer a "course" of parenteral iron consisting of a series of injections (e.g., 250 mg daily × 4) or perhaps a single bolus of 1 to 2 gm intravenously over 3 to 4 hours.

Various parenteral fluids have a negligible iron content, and daily intravenous iron administration is not recommended.

Recommendations for Solutions

The various approaches to parenteral iron therapy have been outlined in detail elsewhere.[12] Iron salts cannot be administered parenterally. There are two parenteral preparations in general use at the present time. Iron dextran (Imferon) is a high molecular weight complex of ferric hydroxide and dextran that can be given by either intramuscular or intravenous infusion. This preparation has been widely used but has the disadvantage that systemic allergic reactions may occur such as fever, joint pain, and lymphadenopathy.[21] Anaphylaxis following Imferon is uncommon but has caused several deaths.[22] At one time the drug was withdrawn because of evidence in rats that sarcoma could be induced by intramuscular Imferon, but this does not occur in man.

Iron sorbitol citrate (Jectofer) has the clinical advantage that it is absorbed more rapidly from the site of intramuscular injection and produces little if any staining of the skin. However, the iron is less firmly complexed and 30 to 50% of each dose is excreted in the urine, making calculations of the administered amount more difficult. This urinary iron loss may be accompanied by an exacerbation of urinary tract infection.

A new iron preparation, Ferastral, has been introduced recently but is still undergoing clinical trial.[23] The most important advantage of this preparation is that allergic reactions apparently do not occur. Initial reports suggest that this may ultimately prove to be the best form of iron for parenteral administration.

REFERENCES

1. Dallman, P. R., Beutler, E., and Finch, C. A.: Effect of iron deficiency exclusive of anaemia. *Br. J. Haemat. 40:* 179-84, 1978.
2. Finch, C. A., Miller, L. R., Inamdar, A. R., et al.: Iron deficiency in the rat. Physiological and biochemical studies of muscle dysfunction. *J. Clin. Invest. 58:* 447-53, 1976.
3. Webb, T. E. and Oski, F. A.: Iron deficiency anemia and scholastic achievement. *J. Ped. 83:* 827-30, 1973.
4. Webb, T. E. and Oski, F. A.: Behavioral status of young adolescents with iron deficiency anemia. *J. Special Ed. 8:* 153, 1974.
5. Johnson, D. H. M., Jacobs, A., Murray-Walker, D., and Dolby, A. E.: Defect of cell-mediated immunity in patients with iron deficiency anemia. *Lancet 2:* 1058-59, 1972.
6. MacDougall, L. G., Anderson, R., McNab, G. M., and Katz, J.: The immune response in iron deficient children: impaired cellular defense mechanisms with altered humoral components. *J. Ped. 86,* 833-43, 1975.
7. Prasad, J. S.: Leucocyte function in iron deficiency anemia. *Amer. J. Clin. Nutr. 32,* 550-52, 1979.
8. Dillman, E., Gale, C., Green; W., et al.: Hypothermia in iron deficiency due to altered triiodothyronine metabolism. *Am. J. Physiol. 239:* R377-81, 1980.
9. Committee on Nutrition, American Academy of Pediatrics: Iron supplementation for infants. *Pediatrics 58:* 765-68, 1976.
10. FAO/WHO Expert Group: Requirements of ascorbic acid, vitamin D, vitamin B_{12}, folate, and iron. World Health Organization Technical Report Series No. 452, 1970.
11. Takkunen, H.: Iron deficiency in the Finnish adult population: an epidemiological survey from 1967-1972 inclusive. *Scand. J. Haematol.* (Suppl.) *25:* 1-91, 1976.
12. Bothwell, T. H., Charlton, R. W., Cook, J. D., and Finch C. A.: *Iron Metabolism in Man.* Oxford, Blackwell, 1979, pp. 1-576.
13. Bjorn-Rasmussen, E., Hallberg, L., Isaksson, B., and Arvidsson, B.: Food iron absorption in man. Application of the two-pool extrinsic tag method to measure heme and non-heme iron absorption from the whole diet. *J. Clin. Invest. 53:* 247-55, 1974.
14. Green, R., Charlton, R. W., Seftel, H., et al.: Body iron excretion in man. A collaborative study. *Am. J. Med. 45:* 336-53, 1968.
15. Cole, S. K., Billewicz, W. Z., and Thomson, A. M.: Sources of variation in menstrual blood loss. *J. Obstet. Gynaec. Br. Common. 78,* 933-39, 1971.
16. Hallberg, L., Hogdahl, A. M., Nilsson, L., and Rybo, G.: Menstrual blood loss – a population study. Variation at different ages and attempts to define normality. *Acta Obstet. Gynaec. Scand. 45:* 320-51, 1966.
17. Bothwell, T. H. and Charlton, R. W.: *Iron Deficiency in Women. A Report Prepared for the International Nutritional Anemia Consultative Group (INACG).* New York, The Nutrition Foundation, 1981, pp. 1-57.
18. Siimes, M. A., Vuouri, E., and Kuitenen, P.: Breast milk iron – a declining concentration during the course of lactation. *Acta Paed. Scand. 68:* 29-31, 1979.
19. Edwards, C. Q., Skolnick, M. H., and Kushner, J. P.: Hereditary hemochromatosis: contributions of genetic analyses. *Progr. Hematol. 12:* 43-72, 1981.
20. Gokal, R., Millard, P. R., Weatherall, D. J., et al.: Iron metabolism in haemodialysis patients. *Q. J. Med 191:* 369-91, 1979.
21. Shafer, A. W. and Marlow, A. A.: Toxic reaction to intramuscular injection of iron. *New Engl. J. Med. 260:* 180, 1959.
22. Becker, C. E., MacGregor, R. R., Walker, K. S., and Jandl, J. H.: Fatal anaphylaxis after intramuscular iron-dextran. *Ann. Int. Med. 65:* 745-48, 1966.
23. Fielding, J, editor: Ferastral: Iron poly (sorbitol-gluconic acid) complex. Proceedings of a conference, London, 1976. Copenhagen, Monskgaard, 1977, pp. 1-399.