Zinc-Induced Copper Deficiency

HARRY N. HOFFMAN, II,* ROBERT L. PHYLIK Y, and 
C. RICHARD FLEMING
Divisions of Gastroenterology and Hematology, Department of Internal Medicine, Mayo Clinic 
and Mayo Foundation, Rochester, Minnesota

Copper deficiency was found in an adult patient who had received excessive daily oral zinc for 10 mo. The deficiency was characterized by hypochromic-microcytic anemia, leukopenia, and neutropenia. Although initially thought to be caused by iron deficiency, the anemia did not respond to oral or intravenous iron. Cessation of zinc tablets and ingestion of an oral copper preparation daily for 2 mo failed to correct the anemia or leukopenia. It was not until shortly after intravenous administration of a cupric chloride solution during a 5-day period, at a total dose of 10 mg, that serum copper and ceruloplasmin levels increased and the anemia, leukopenia, and neutropenia resolved. These data suggest that the elimination of excess zinc is slow and that, until such elimination occurs, the intestinal absorption of copper is blocked.

Copper is an essential trace element and a component of numerous key metalloenzymes and proteins that are vitally involved in hematopoiesis, in the structure and function of the central nervous system and skeletal and vascular tissues, and in the metabolism of catecholamines. Copper is widely distributed in food sources, and the daily requirement for copper is sufficiently low that copper deficiency in adult humans due to inadequate diet alone probably does not occur. However, nutritional copper deficiency has been observed in infants and in adult patients receiving total parenteral nutrition (1-6).

Dietary zinc and oral zinc therapy interact with copper in a competitive manner in the gut and can produce hypocupremia and increased fecal loss of copper (7-11). In many animal species, including humans, copper deficiency is characterized by hypochromic-microcytic anemia and neutropenia (12-14). There have been only three clinical reports to date of zinc-induced copper deficiency in humans. Prasad et al. (15) described hypocupremia, low serum ceruloplasmin level, hypochromic-microcytic anemia, and neutropenia in a patient with sickle cell anemia who was treated with zinc tablets. Pfeiffer and Jenny (16) described a similar clinical pattern in a young man given large doses of zinc (5 g/day) by his family in an effort to cure a psychosis. Patterson et al. (17) recently described the appearance of a sideroblastic anemia and leukopenia associated with copper deficiency in a man who for 2 yr had taken large amounts of supplemental zinc; the anemia was corrected after zinc intake was stopped. Negative copper balances and favorable clinical responses have been achieved in several patients with Wilson’s disease whose therapy consisted only of zinc (18-21).

This report describes a patient in whom copper deficiency with anemia and neutropenia occurred during long-term supplemental zinc therapy. It also provides observations concerning copper replacement.

Case Report

A 35-yr-old white woman underwent three gastrointestinal operations between June 1980 and February 1983 for treatment of a gastric ulcer, for treatment of alkaline reflux gastritis, and for correction of obstruction and ulceration of her gastrojejunal anastomosis, respectively.

In late 1982, she complained of painful aphthous ulcers of her mouth and tongue. Although they responded temporarily to short courses of corticosteroids, the ulcers recurred during the next several months. In April 1983, she was advised by a dermatologist to take supplemental zinc. Beginning in April 1983 and continuing for 10 mo, she ingested 440-660 mg of zinc sulfate (110-165 mg of elemental zinc) daily, as well as one zinc-containing (80 mg of zinc sulfate) vitamin preparation daily. (The recommended daily allowance for the oral intake of zinc is 15 mg.) The serum zinc value was 0.63 μg/dl (normal 0.66-1.10 μg/dl) and serum copper was 0.6 μg/dl (normal

Abbreviation used in this paper: MT, metallothionein.
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Figure 1. Levels of hemoglobin, mean corpuscular volume, and leukocyte count during zinc therapy and after zinc therapy was discontinued and copper therapy was initiated. Shaded areas represent the normal ranges.

0.75–1.45 μg/dl) before she began taking supplemental zinc. At the start of zinc therapy in April 1983, her hemoglobin was 11.8 g/dl, erythrocytes 3,970,000/μl, hematocrit 34.8%, mean corpuscular volume 87.6 fl, and platelets 377,000/μl. Leukocytes were 7100/μl with 63% neutrophils, 22% lymphocytes, 10% monocytes, and 3% eosinophils. The oral ulcers became less frequent and troublesome while taking oral zinc.

During the next several months, the patient was noted to have a slowly worsening microcytic-hypochromic anemia (Figure 1). Tests for occult fecal blood loss were consistently negative, and barium examinations of her entire gastrointestinal tract as well as gastroscopy showed no abnormalities. Hence, it was assumed that the anemia was due to impaired iron absorption or inadequate repletion of the iron stores, or both, as a consequence of the three gastric operations, although no serum iron or ferritin measurements were done at that time. However, the anemia did not respond to a 6-mo course of oral ferrous sulfate (325–975 mg/day), nor did it respond to intramuscular iron dextran (1025 mg of elemental iron). Bone marrow examination after the iron therapy showed normal cellularity with a low myeloid to erythroid ratio, slight hypochromia, the presence of stainable iron, and an absence of ringed sideroblasts. Serum ferritin was 96 μg/ml and reticulocytes were 1.4%.

In February 1984, the serum zinc concentration was elevated to 1.44 μg/dl, the serum copper level was low at 0.15 μg/dl, and the serum ceruloplasmin was 0 [normal 22.9–43.1 mg/dl]. Urinary zinc excretion for 24 h was 3500 μg [normal 300–600 μg], and urinary copper excretion was 11 μg/24 h [normal 15–60 μg/24 h]. At that time, the hemoglobin level was 10.2 g/dl, mean corpuscular volume 63 fl, mean corpuscular hemoglobin 21.9 pg, and mean corpuscular hemoglobin concentration 31.1%. The leukocyte count was 2000/μl with 38% segmented neutrophils, 50% lymphocytes, 6% monocytes, 5% eosinophils, and 1% basophils. Reticulocytes were 1.3% (see Figure 1).

The findings suggested a conditioned copper deficiency. Zinc and iron therapy were discontinued and the patient received an oral preparation that provided 2 mg of elemental copper per day. During the next 2 mo there was no improvement of the hematologic abnormalities, the ceruloplasmin remained low, and the urinary zinc excretion ranged from 3500 to 4500 mg/24 h (Figures 1 and 2).

Discussion with the patient and examination of her medications failed to reveal any nondietary sources of zinc during this period.

In April 1984, cupric chloride solution (0.4 mg/ml) was given intravenously during a 5-day period for a total dose of 10 mg. Two weeks later, the ceruloplasmin level had...
crease copper sequestration in the mucosal cell. Copper can depress zinc absorption. Copper has been observed in zinc-deficient animals, and high dietary copper absorption (23,24). Whereas zinc MT has a half-life of 18-20 h, copper MT is more durable and resistant to proteolysis. These mutually antagonistic effects, however, are not noted with physiologic levels of dietary zinc and copper and thus appear to require more striking dietary imbalances in copper and zinc before they become clinically apparent.

It is not known precisely when hypocupremia actually began in our patient, but it occurred during the several months she was taking supplemental zinc. Declining values for hemoglobin and mean corpuscular volume were first noted 6-8 wk after zinc treatment was begun in April 1983. In healthy adults fed supplemental zinc and copper, Abdulla (25) noted low plasma levels of copper and low copper to zinc ratios after 2 wk of this treatment. Rats fed a diet high in zinc showed a large decrease in serum ceruloplasmin level after 15 days. Brewer et al. (18) reported that in his patients with Wilson's disease who had received prior penicillamine therapy, it was necessary to administer zinc orally during a longer period to replete the low zinc stores in the body before the induction of MT synthesis and resultant inhibition of copper absorption could be noted.

When anemia and microcytosis were first noted in our patient, we assumed that she was probably iron-deficient because of her gastric operations and impaired iron absorption. Serum iron was only marginally low, and ferritin was not measured. However, several months of oral and subsequent intramuscular administration of iron did not alter the slow downward course of the hemoglobin and mean corpuscular volume values or prevent the appearance of leukopenia and neutropenia. Gastrointestinal blood loss was ruled out by radiologic, endoscopic, and stool studies. Iron in the bone marrow was largely confined to reticuloendothelial cells. Although optimal investigation was not done, it is unlikely that clinically significant malabsorption was present because (a) the patient had gained weight after her gastric operations, (b) two stool examinations for excess fat were negative, and (c) serum values for carotene and prothrombin time were normal. Unfortunately, laboratory data regarding body iron status before and during the several months she was taking supplemental iron were not available. Although optimal investigation was not done, it is unlikely that clinically significant malabsorption was present because (a) the patient had gained weight after her gastric operations, (b) two stool examinations for excess fat were negative, and (c) serum values for carotene and prothrombin time were normal. Unfortunately, laboratory data regarding body iron status before and during the several months she was taking supplemental iron were not available.

The failure of oral copper therapy (2 mg/day) to produce a hematologic response was unexpected and puzzling until the persistently high serum and urinary zinc levels were noted. We assumed that her
total body zinc pool was sufficiently high to block intestinal copper absorption. It was not until shortly after copper was given intravenously that serum copper and ceruloplasmin levels began to increase and the anemia improved. We are not aware of data indicating the rate of mobilization of excessive body stores of zinc in humans, but our studies suggested that the elimination of excess zinc is slow and that, until such elimination occurs, the intestinal absorption of oral copper is blocked.

The role of copper in hematopoiesis is not fully understood, but much evidence from animal studies suggests that ceruloplasmin is a molecular link between iron and copper metabolism at the level of iron mobilization from cellular storage sites to plasma. Ceruloplasmin, a true oxidase or ferredoxin, plays a major role in oxidizing ferrous iron to the ferric form. This is necessary for the uptake of iron from intestinal mucosa by transferrin to the hepatic parenchymal and reticuloendothelial cells and for the movement of iron to the bone marrow for heme synthesis (26–29). When plasma ceruloplasmin levels are greatly lowered, iron metabolism is significantly impaired and hypoferrinemia has been noted. These defects have been shown to be promptly correctable in animals by the exogenous infusion of ceruloplasmin or, after the eventual restoration of ceruloplasmin levels, by the administration of inorganic copper. However, intramuscular injections of iron have no effect on the anemia (12,13).

Impaired heme synthesis also occurs in copper deficiency anemia, perhaps because of decreased activity of the cuproenzyme cytochrome oxidase, which is required for iron uptake by mitochondria where the heme synthetase reaction occurs in heme biosynthesis (30). Evidence has also been presented for a copper-dependent plasma factor needed for normal bone marrow cell growth (14).

Although our knowledge of the spectrum of clinical, biochemical, and pathophysiologic manifestations of copper deficiency has been gained primarily from animal studies, human copper deficiency has most often been characterized only by anemia, neutropenia, hypocupremia, and hypoceruloplasminemia. The peripheral blood picture has most commonly shown a hypochromic anemia associated with a decreased reticulocyte count, and normal serum iron and total iron binding capacity. A variety of bone marrow features have been described. Iron has usually been present, and ringed sideroblasts have been observed in several cases (18). In our case, sideroblasts were present, and ringed forms were not observed. Our case resembles a case reported by Patterson et al. (17) in the slow recovery of the hypocupremia and neutropenia and return of the serum zinc level to normal despite cessation of zinc intake.

In summary, we have presented a case of adult copper deficiency induced by excessive daily oral zinc and characterized by hypocupremia, hypoceruloplasminemia, hypochromic and microcytic anemia, leukopenia, and neutropenia.

References

*Deceased.*