Toxic Effects Associated With Consumption of Zinc

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A 27-year-old man with a history of acne presented to his primary care physician because of fatigue and dyspnea on exertion of 4 weeks’ duration. He was remarkably pale, orthostatic pulse changes were noted, and a systolic ejection murmur was heard. The patient had profound anemia (hemoglobin concentration, 5.0 g/dL) and neutropenia (neutrophil count, 0.06 × 10^9/L); he was admitted for further evaluation. A detailed inquiry into his medication history revealed that he was taking several vitamins and zinc gluconate, 850 to 1000 mg/d for 1 year (US recommended daily allowance, 15 mg), as therapy for acne. A zinc toxic and copper-deficient state was confirmed by laboratory studies. The patient was treated with intravenous copper sulfate, followed by 3 months of oral therapy. The complete blood cell count, serum copper level, and serum zinc level returned to normal.

Dietary supplements have increased in both popularity and sales. In the United States, they are used by about half of the adult population. Americans spent $6.5 billion on dietary supplements in 1996 and were projected to spend $14 billion in 2000. Passage of the Dietary Supplement Health and Education Act in 1994 deregulated the supplement industry and most likely contributed to this trend, which is further fueled by growth in Internet retail. Media reports based on confusing literature, patients’ distrust of physicians, aggressive marketing strategies by manufacturers, and an increasing desire for defying age and gaining a competitive edge also contribute to the popularity of dietary supplements. Therefore, patients presenting to their health care providers are increasingly likely to use supplements that they believe are “safe” and “natural.” The following case of zinc toxicity supports the fallacy of such presumptions and cautions primary care physicians to pay attention to the dose and the variety of supplements that their patients are taking.

Zinc and copper are essential trace elements whose roles in metabolism have been studied extensively. These elements are available from a wide variety of food sources, and dietary deficiency of either is rare in a typical American diet. Copper in the form of ceruloplasmin acts as a cofactor in the reaction that mobilizes iron stores needed for hemoglobin synthesis; therefore, copper deficiency leads to anemia. Zinc supplements gained popularity as a remedy for the common cold (zinc lozenges), to promote healing of skin ulcers, and to treat macular degeneration. However, scientific evidence for these therapeutic effects remains weak. Zinc therapy also has been used to treat inflammatory acne with mixed success. Randomized placebo-controlled trials of zinc therapy for acne showed a marginal therapeutic effect. These studies were plagued by small patient populations, difficulties in quantification of clinical benefits, and large placebo effects. Additionally, in a recent comparative trial with oral minocycline, oral zinc was inferior.

Copper deficiency secondary to excessive zinc intake has been well described in patients taking large doses of supplemental zinc for treatment of sickle cell anemia, aphthous ulcers, and prostate cancer, as well as in zinc coin ingestion. These patients uniformly presented with signs and symptoms of anemia. On further evaluation, patients with zinc toxicity had neutropenia and anemia of either the microcytic or sideroblastic variety.

Zinc and copper have a competitive absorption relationship within enterocytes mediated by metallothionein, a zinc- and copper-binding protein that binds copper with greater affinity than zinc. Zinc and copper are either bound to metallothionein and stored inside enterocytes or exist in an unbound state. Bound complexes are shed intraluminally and excreted as enterocytes turn over. Unbound zinc and copper are absorbed into the portal circulation.

Metallothionein expression is regulated by dietary zinc content alone. When large amounts of dietary zinc are ingested, metallothionein expression increases, more zinc is bound to metallothionein, and more zinc-metallothionein complexes are excreted. Because of the difference in binding affinities between zinc and copper (copper binds metallothionein with greater affinity), a potential for pro-
nounced copper excretion exists. Therefore, a substantial increase in zinc ingestion potentially would cause a dramatic decrease in copper absorption.

REPORT OF A CASE
A 27-year-old man with no remarkable medical history presented to his primary care physician because of fatigue and dyspnea on exertion of 4 weeks’ duration. He was unable to work for 7 days due to weakness. The patient had no fever or recent infectious symptoms, but he recalled a single episode of night sweats 1 week before admission. Initially, he admitted to taking a daily multiple vitamin, along with vitamin E, vitamin A, topical benzoyl peroxide, and occasionally ginseng. He was taking no prescription medications. His father died of coronary artery disease at age 72 years, and his mother has breast cancer. The patient is a commodity stock trader, nonsmoker, and binge drinker (10 beers per weekend) who has no risk factors for human immunodeficiency virus (HIV). A review of systems was remarkable for a 4.5-kg weight loss during the past month.

On physical examination, the patient’s pulse was 88 beats/min, blood pressure was 100/50 mm Hg, respirations were 14/min, and temperature was 37.8°C. His conjunctivae and skin were remarkably pale, and no facial pustules or comedones were noted. He had a systolic ejection murmur radiating to his neck. The patient had no hepatomegaly, splenomegaly, or palpable lymph nodes, and stool from a rectal examination was negative for occult blood.

The patient’s initial complete blood cell count was remarkable for hemoglobin of 5.0 g/dL, hematocrit of 14.7%, total leukocyte count of 1.2 × 10⁹/L (5% neutrophils, 70% lymphocytes, 25% monocytes), and a mean corpuscular volume of 85.7 fl. Liver function panel, electrolyte level, and heterophile antibody test were normal; findings on an electrocardiogram and a chest radiograph were normal. He was admitted for further evaluation.

A more focused inquiry into the patient’s medication history revealed that he had been taking the following nutritional supplements: vitamin E, 1200 IU/d; vitamin A, 60,000 IU/d; 1 multiple vitamin tablet a day; and zinc gluconate, 850 to 1000 mg/d for the past year (recommended daily allowance, 15 mg). A year before presentation the patient saw a chiropractor for back pain and acne. He was referred to a textbook of remedies in the chiropractor’s office from which he learned that zinc and vitamin A are therapeutic for acne. He also read that zinc may cause copper deficiency as an adverse effect but elected to take daily zinc gluconate treatment in low doses. After several weeks of poor response, the patient dramatically increased the dose to more than fifteen 50-mg tablets and noted substantial improvement in his acne.

On admission, the patient’s serum zinc level was 3.18 µg/mL (reference range shown parenthetically) (0.66-1.10 µg/mL), serum copper level was 0.10 µg/mL (0.75-1.45 µg/mL), and serum ceruloplasmin was less than 10 mg/dL (22-61 mg/dL) (zinc and copper levels were measured by Mayo Medical Laboratories, Rochester, Minn). His reticulocyte count was zero per high-power field, and serum vitamin B₁₂, red blood cell folate, and iron studies were normal. Immunologic assays for hepatitis B, hepatitis C, and HIV were negative. The patient declined to undergo a bone marrow biopsy, but the peripheral blood smear was unremarkable except for neutropenia, microcytosis, and absence of ringed sideroblasts.

Initially, the patient was placed on neutropenic precautions (strict hand washing, private room, no fresh fruits or vegetables), and zinc was discontinued. Neoplastic and infectious etiologies were strongly considered until the patient admitted to taking large doses of zinc. Thereafter, copper sulfate was initiated intravenously at 2 mg/d.¹⁸ On day 2 of hospitalization, the patient had an episode of neutropenic fever and was empirically treated with intravenous cefazidime and gentamicin. The evaluation of neutropenic fever included a lumbar puncture that was unrevealing and computed tomography of the sinuses that revealed right frontal sinus opacification consistent with acute sinusitis. From day 2 to day 9, the patient was treated with pseudoephedrine and oxymetazoline nasal spray, and intravenous clindamycin was added for anaerobic coverage of sinusitis. Repeated evaluations by an otolaryngologist were unremarkable. Despite intravenous copper therapy, the patient’s zinc level, copper level, and red and white blood cell counts remained the same. He also remained febrile. Subcutaneous human granulocyte colony-stimulating factor was administered from day 5 to day 9, which dramatically raised his white blood cell count and aided in resolution of his neutropenic fever. Before discharge on day 9, the patient was given a transfusion of 2 U of packed red blood cells, his antibiotic regimen was changed to oral amoxicillin/clavulanic acid, and the copper sulfate was changed to an oral regimen (10 mg/d for the first 10 days followed by 2 mg/d for 10 weeks). During the next 3 months, the complete blood cell count, serum copper levels, and zinc levels returned to normal (Figure 1). However, at follow-up the patient admitted to continuing to take zinc supplements because his acne had worsened. He was strongly cautioned against this and was given topical antibiotics instead. To our knowledge, he stopped taking zinc supplementation thereafter.

DISCUSSION
We want to emphasize 2 important points from this case of zinc toxicity. First, patients taking large doses of dietary
supplementation.

Tom, As expected, serum zinc and copper levels measured over time due to human granulocyte colony-stimulating factor therapy. Blood cells. The rapid rise in WBC count at the same time is followed by 10 mg PO per day for 10 days, and finally 2 mg PO per day for 70 days. The steep rise in Hct levels on day 7 (arrow) indicates that up to 61% of outpatients seen at Mayo Clinic, Rochester, Minn, use dietary supplements; however, only half of those provided that information in the initial history, and the other half admitted to it only after answering a detailed questionnaire. In fact, dietary supplements often are not considered medications or drugs by patients or physicians, and such supplements are clearly subjected to less scrutiny by the Food and Drug Administration. There-