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Zinc

Updated: January 10, 2015.

OVERVIEW

Introduction

Zinc is an essential mineral and heavy metal that is included in most over-the-counter multivitamin and mineral supplements, and is used therapeutically in higher doses because of its ability to block copper absorption as maintenance therapy of Wilson disease. Zinc has not been associated with worsening of serum enzyme elevations during therapy or with clinically apparent liver injury.

Background

Zinc is an essential trace element that is found in many human enzymes and transcription factors. The recommended dietary allowance is 8 mg per day for women and 11 mg for men. Zinc is widely present in foods, and the typical Western diet has adequate concentrations, the highest levels being found in shellfish and red meats. Zinc deficiency is usually due to malnutrition and reduced dietary intake, but can also occur with strict vegetarian diets. Zinc deficiency is not uncommon in developing countries, but severe deficiencies are rare. Zinc deficiency can be accompanied by growth retardation, infertility, dysgeusia, diarrhea, dermatitis, glossitis, behavioral changes, depression and mental clouding. The recommended daily allowance of zinc is 15 mg per day in men and 12 mg in women, with higher levvels recommended for pregnant or lactating women.

High doses of oral zinc interfere with the absorption of copper and iron, and supplementation above the RDA can cause copper deficiency. Because of its effects on copper balance, zinc has been used to treat Wilson disease, particularly as maintenance therapy once copper levels have been reduced with chelating agents. Wilson disease is a caused by inherited mutation in the ATPase7B gene, which encodes a hepatic enzyme responsible for the transmembrane transport and excretion of copper. The metabolic defect leads to accumulation of free copper in liver and blood and secondarily in other organs, particularly brain and kidney. The disease usually presents in childhood or adolescence with neurologic syndromes, signs of advanced liver disease and hemolytic anemia. Zinc is a unique approach to the treatment of Wilson disease in that it interferes with dietary absorption (probably by increasing intestinal metallothionein), rather than decreasing tissue levels by chelation. Zinc acetate is approved for use in the United States as maintenance therapy of Wilson disease and is available in capsules of 25 and 50 mg under the brand name Galzin. Other zinc formulations have been used to treat Wilson disease, including zinc sulfate and zinc gluconate (Gluzin), but these have not been formally approved for this indication. The recommended dose is 25 to 50 mg two to three times daily. Zinc when given only one daily has little or no effect on copper balance, and is not recommended. Zinc is generally well tolerated, but when given in high doses up to 10% of patients initially have abdominal pains or gastrointestinal intolerance which can require dose adjustment or discontinuation. Long term therapy can potentially lead to copper deficiency.

Zinc overdose has been described and is usually due to ingestion of coins, metallic objects or zinc soldering solutions and rarely to suicidal overdose. Symptoms include rapid onset of epigastric pain, nausea and vomiting and diarrhea, followed by lethargy, dizziness, ataxia, confusion and coma. With high doses, patients develop hypotension, metabolic acidosis and hemolytic anemia that can be severe and life-threatening. Liver injury is generally mild and arises after a day or two. Nevertheless, cases with jaundice, cholestasis and hepatic failure have been described. Therapy of acute zinc overdose generally rests upon hydration, gastric lavage or whole bowel irrigation, correction of metabolic acidosis and anemia and zinc chelation with dimercaprol or EDTA infusions.

Hepatotoxicity

In case series and small trials of zinc therapy in patients with Wilson disease, adverse events have included gastrointestinal upset, but serum enzyme elevations and clinically apparent liver injury were not reported. Patients with Wilson disease frequently have liver injury and, in most case series, zinc therapy has been associated with slow improvement in the hepatic manifestations.

Zinc overdose can be associated with liver injury, jaundice and even hepatic failure, usually arising after several days and resembling injury from copper or iron overdose. The injury is clearly direct toxicity.

Drug Class: Chelating Agents, Trace Elements and Metals, Wilson Disease Agents

Other Drugs in the Subclass, Wilson Disease: Dimercaprol, Penicillamine, Trientine

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Zinc – Generic, Galzin®

DRUG CLASS

Minerals; Chelating Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Zinc	7440-66-6	Zn	Zn

ANNOTATED BIBLIOGRAPHY

References updated: 10 January 2015

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Review of hepatotoxicity published in 1999; zinc is not discussed).

Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013.

(Textbook on hepatotoxicity; agents for Wilson disease are not discussed).

Byrns MC, Penning TM. Treatment of metal exposure. Environmental toxicology: carcinogens and heavy metals. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1872-6.

(Textbook of pharmacology and therapeutics).

Murphy JV. Intoxication following ingestion of elemental zinc. JAMA 1970; 212: 2119-20. PubMed PMID: 5467786.

(16 year old boy ingested 12 g of elemental zinc to help healing of a skin laceration and developed lethargy, light-headedness and ataxia which responded to hydration and dimercaprol [BAL] therapy; serum aminotransferase and bilirubin levels were normal).

Brocks A, Reid H, Glazer G. Acute intravenous zinc poisoning. Br Med J 1977; 1 (6073): 1390-1. PubMed PMID: 405076.

(72 year old woman on total parenteral nutrition was given an overdose of zinc sulfate [7.4 g] and she developed hypotension, diarrhea, vomiting, oliguria and jaundice with a cholestatic pattern that slowly resolved, but she died of pneumonia 47 days later).

Stowe CM, Nelson R, Werdin R, Fangmann G, Fredrick P, Weaver G, Arendt TD. Zinc phosphide poisoning in dogs. J Am Vet Med Assoc 1978; 173: 270. PubMed PMID: 689968.

(Six cases of zinc toxicity in dogs due to zinc phosphide, a rodenticide, presenting with malodor, tremors, rigidity and seizures; no mention of liver injury).

Potter JL. Acute zinc chloride ingestion in a young child. Ann Emerg Med 1981; 10: 267-9. PubMed PMID: 6784612.

(28 month old boy ingested 4 ounces of soldering flux [20% zinc chloride] and rapidly developed vomiting and lethargy followed by metabolic acidosis [zinc 1,644 µg/dL, AST 48 U/L, Alk P 197 U/L], recovering within 2 days with hydration and EDTA infusions).

Chobanian SJ. Accidental ingestion of liquid zinc chloride: local and systemic effects. Ann Emerg Med 1981; 10: 91-3. PubMed PMID: 6784611.

(24 year old man accidentally ingested a zinc chloride solution with immediate vomiting and burning pain which resolved within 3 days with hydration and EDTA therapy; serum bilirubin and liver enzymes remaining normal).

Hornfeldt CS, Koepke TE. A case of suspected zinc toxicity in a dog. Vet Hum Toxicol 1984 Jun; 26 (3): 214. PubMed PMID: 6610246.

(Ordered: 11.21.2014).

Allen JG, Masters HG, Peet RL, Mullins KR, Lewis RD, Skirrow SZ, Fry J. Zinc toxicity in ruminants. J Comp Pathol 1983; 93: 363-77. PubMed PMID: 6886083.

(In sheep and cattle, zinc toxicity can arise from use of galvanized troughs or zinc containing fertilizers or fungicides, presenting with diarrhea and vomiting, weakness and jaundice and death in severely affected animals, autopsies showing centrolobular [zone 3] hepatic necrosis).

Ulmer DD. Trace elements. N Engl J Med 1977; 297: 318-21. PubMed PMID: 876314.

(Brief review of trace elements, their metabolic roles, deficiencies and toxicities).

Hoogenraad TU, Van den Hamer CJ, Koevoet R, Korver EG. Oral zinc in Wilson's disease. Lancet 1978; 2 (8102): 1262. PubMed PMID: 82772.

(16 year old with Wilson disease had cupruresis on penicillamine after failure during zinc therapy, although he had no clinical improvement until zinc was reintroduced).

Brewer GJ, Hill GM, Prasad AS, Cossck ZT, Rabbani P. Oral zinc therapy for Wilson.s disease. Ann Intern Med 1983; 99: 314-20. PubMed PMID: 6614680.

(5 patients [25-34 years old, 3 men, 2 women] with stable Wilson disease after penicillamine therapy underwent careful copper balance studies while on zinc therapy alone, demonstrating a negative copper balance largely due to increased fecal loss).

Hoogenraad TU, Van den Hamer CJ. 3 years of continuous oral zinc therapy in 4 patients with Wilson's disease. Acta Neurol Scand 1983; 67: 356-64. PubMed PMID: 6613522.

(4 patients [17-46 year old men] with Wilson disease previously treated with penicillamine were treated with oral zinc for at least 3 years and all showed clinical improvement and no adverse events, including no changes in liver tests during zinc therapy).

Hill GM, Brewer GJ, Juni JE, Prasad AS, Dick RD. Treatment of Wilson's disease with zinc. II. Validation of oral 64copper with copper balance. Am J Med Sci 1986; 292: 344-9. PubMed PMID: 3799705.

(Assessment of copper update using a radioactive copper uptake study demonstrated that patients with Wilson disease on zinc have a low [<1%], while those on no therapy or on penicillamine or trientine had normal update levels [~6%]).

Breitschwerdt EB, Armstrong PJ, Robinette CL, Dillman RC, Karl ML, Lowry EC. Three cases of acute zinc toxicosis in dogs. Vet Hum Toxicol 1986; 28: 109-17. PubMed PMID: 3705436.

(3 dogs with zinc toxicity, 2 from swallowing zinc nuts and one from licking zinc oxide ointment, presenting with vomiting, fever, pallor and jaundice with severe hemolytic anemia [bilirubin 1.7-14.9 mg/dL, ALT 143-159 U/L, Alk P 448-5400 U/L], 2 recovering and one dying of anemia and sepsis).

Torrance AG, Fulton RB Jr. Zinc-induced hemolytic anemia in a dog. J Am Vet Med Assoc 1987; 191: 443-4. PubMed PMID: 3654320.

(1 year old Yorkie developed diarrhea, vomiting, fever and "depression" with severe anemia [hematocrit 15%] after ingesting a zinc nut from his cage [bilirubin 18.9 mg/dL, Alk P 1262 U/L], recovering after endoscopic removal of object).

Hill GM, Brewer GJ, Prasad AS, Hydrick CR, Hartmann DE. Treatment of Wilson's disease with zinc. I. Oral zinc therapy regimens. Hepatology 1987; 7: 522-8. PubMed PMID: 3570163.

(Copper balance studies in 14 patients with previously treated Wilson disease showed a negative copper balance while on zinc [100-150 mg daily in 2-4 separate doses] compared to high positive copper balance in 3 patients on no therapy; no adverse events noted).

Hoogenraad TU, Van Hattum J, Van den Hamer CJ. Management of Wilson.s disease with zinc sulphate: experience in a series of 27 patients. J Neurol Sci 1987; 77: 137-146. PubMed PMID: 3819764.

(Among 27 Dutch patients [ages 11-38 years] with Wilson disease treated with zinc sulfate for periods of 1 month to 27 years, 1 died of hepatic failure within the first month, the others all improved with normalization of free serum copper levels and no adverse events).

Burkhart KK, Kulig KW, Rumack B. Whole-bowel irrigation as treatment for zinc sulfate overdose. Ann Emerg Med 1990; 19: 1167-70. PubMed PMID: 1977339.

(16 year old boy ingested 50 zinc sulfate tablets in a suicide attempt and was treated with emetics and whole bowel irrigation, with recovery in 2 days and no mention of liver injury or enzyme elevations).

Broun ER, Greist A, Tricot G, Hoffman R. Excessive zinc ingestion. A reversible cause of sideroblastic anemia and bone marrow depression. JAMA 1990; 264: 1441-3. PubMed PMID: 2094240.

(Two patients developed anemia due to zinc; a 31 year old schizophrenic man swallowed multiple coins and presented with nausea and abdominal pain with subsequent severe anemia resolving within 4 weeks; a 48 year old man on chronic zinc supplements developed fatigue and severe anemia, resolving within 2 weeks of stopping zinc intake; no mention of liver injury).

Brewer GJ, Yuzbasiyan-Gurkan V, Johnson V, Dick RD, Wang Y. Treatment of Wilson's disease with zinc XII: dose regimen requirements. Am J Med Sci 1993; 305: 199-202. PubMed PMID: 8475943.

(Analysis of copper balance in 4 patients treated with 75 mg of zinc daily in 1, 2 or 3 divided doses indicated that once daily regimen did not reliably result in a negative copper balance, suggesting that zinc must be given in divided doses 2 or 3 times daily).

McKinney PE, Brent J, Kulig K. Acute zinc chloride ingestion in a child: local and systemic effects. Ann Emerg Med 1994; 23: 1383-7. PubMed PMID: 7515217.

(16 month old boy ingested zinc chloride soldering solution and developed vomiting and lethargy with metabolic acidosis and liver test abnormalities [bilirubin normal, ALT 123 U/L, Alk P 527 U/L], resolving within 3 days, but with severe anemia lasting a week).

Brewer GJ, Dick RD, Johnson VD, Brunberg JA, Kluin KJ, Fink JK. Treatment of Wilson's disease with zinc: XV long-term follow-up studies. J Lab Clin Med 1998; 132: 264-78. PubMed PMID: 9794697.

(Description of patterns of change in urinary, hepatic and serum copper and zinc levels and liver tests in 141 patients with Wilson disease treated with zinc; adverse reactions were "minimal", the most common being initial abdominal discomfort).

Anderson LA, Hakojarvi SL, Boudreaux SK. Zinc acetate treatment in Wilson's disease. Ann Pharmacother 1998; 32: 78-87. PubMed PMID: 9475826.

(Systematic review of the literature on safety and efficacy of oral zinc therapy of Wilson disease concluded that zinc acetate was effective in maintenance of copper balance in patients with Wilson disease and has negligible toxicity).

Ala A, Walker AP, Ashkan K, Dooley JS, Schilsky ML. Wilson's disease. Lancet 2007; 369 (9559): 397-408. PubMed PMID: 17276780.

(Review of the clinical features, pathogenesis, genetics, diagnosis and treatment including role of zinc).

Gurnee CM, Drobatz KJ. Zinc intoxication in dogs: 19 cases (1991-2003). J Am Vet Med Assoc 2007; 230: 1174-9. PubMed PMID: 17501656.

(Retrospective review of 19 cases of zinc toxicosis in dogs seen over an 8 year period at one veterinary hospital; dogs presented with vomiting and lethargy with pallor and jaundice, bilirubin elevations in 80% [0.5-23 mg/dL], ALT in 7% [3-92 U/L], Alk P in 92% [107-1422 U/L] and 2 deaths [10%]; source of zinc being coins, tacks and bolts).

Roberts EA, Schilsky ML, AASLD. Diagnosis and treatment of Wilson disease: an update. Hepatology 2008; 47: 2089-111. PubMed PMID: 18506894.

(Thorough review of the cause, natural history, diagnosis and treatment of Wilson disease, with specific recommendations for use of penicillamine, trientine and zinc).

Linn FH, Howen RH, van Hattum J, van der Kleij S, van Erpecum KJ. Long-term exclusive zinc monotherapy in symptomatic Wilson disease: experience in 17 patients. Hepatology 2009; 50: 1442-52. PubMed PMID: 19731238.

(Among 17 Dutch patients [ages 13-26] with symptomatic Wilson disease treated with zinc only for 2-30 years, most had a clinical response to treatment, but 2 patients with a neurologic presentation developed liver injury after 6 and 7 years of therapy, and 2 patients with cirrhosis initially developed liver decompensation after 15 and 24 years of therapy; the efficacy of copper elimination appeared less in those with hepatic than neurologic presentations).

Walshe JM. The conquest of Wilson's disease. Brain 2009; 132 (Pt 8): 2289-95. *(History of the initial description of Wilson disease, its link to copper accumulation, and therapies several of which were developed by the author* PubMed PMID: 19596747.

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Weiss KH, Stremmel W. Evolving perspectives in Wilson disease diagnosis: treatment and monitoring. Curr Gastroenterol Rep 2012; 14: 1-7. PubMed PMID: 22083169.

(Review of the diagnosis and management of Wilson disease, including the role of genetic testing and the choice of medical therapies).