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ABSTRACT & COMMENTARY

Zinc Supplementation: A Risk for Copper Deficiency

By Martin S. Lipsky, MD

Adjunct Professor, Institute on Aging, School of Community Health, Portland State University; Dean Emeritus, University of Illinois College of Medicine, Rockford

Dr. Lipsky is a retained consultant for Health Solutions & Strategies.

SYNOPSIS: Doctors often misdiagnose zinc deficiency, and patients prescribed high doses of zinc are at risk for iatrogenic copper deficiency.

SOURCE: Duncan A, et al. The risk of copper deficiency in patients prescribed zinc supplements. *J Clin Pathol* 2015.doi: 10.1136/jclinpath-2014-202837 Published online June 17, 2015.

Zinc is essential for health in trace amounts, but the amount of zinc in supplement formulations often exceeds the recommended daily amount.[1] While there is little evidence to suggest that short-term replacement, even with larger doses, is harmful, longer-term usage of high-dose zinc interferes with copper absorption and might cause a copper deficiency associated with anemia, neutropenia, and neurological symptoms.[2]

The study investigators reviewed the charts of 70 patients at Glasgow hospitals taking zinc prescribed by their general practitioner.[1] Surprisingly, only a little more than half of those prescribed zinc were tested and documented as having low serum levels. Among those with low plasma concentrations, some were attributable to hypoalbuminemia or systemic inflammation and did not represent true deficiencies. In only one instance was a clinician aware of a concomitant copper deficiency, and in only two cases did

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Internal Medicine
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clinicians check copper levels.

Among the 70 patients, chart review revealed that 9% developed anemia and 7% developed neurological symptoms suggestive of a copper deficiency. Based on their chart review, the authors concluded zinc deficiency is frequently misdiagnosed based on a low level without considering albumin concentration and/or an inflammatory state. The risk of inducing a copper deficiency is rarely considered, and it appears that a significant minority of patients taking high doses of zinc develop an iatrogenic copper deficiency.

■ COMMENTARY

Physicians often prescribe zinc supplementation in cases of dementia, poor nutrition, alcohol withdrawal, non-healing pressure ulcers, alopecia, recurrent infections, and anosmia. Patients also self-medicate with zinc to strengthen their immune systems, to hasten resolution of a viral syndrome, to prevent recurrent infections, or, unwittingly, in the form of zinc-containing dental fixatives. In the United States, the dose of solvazinc, a commonly used zinc sulphate supplement, contains 45 mg of elemental zinc or an amount in excess of the U.S.-recommended limit of 40 mg/day.[3] True zinc deficiency is rare in the United States, and over a period of months, excessive zinc interferes with copper absorption, which can induce a copper deficiency. Even when clinicians test serum zinc concentrations, they often fail to consider the albumin level or the presence of an inflammatory state.

When I read this article, the number of patients with neurological symptoms, such as tingling and pain induced by zinc supplementation, surprised me. Many clinicians likely view zinc as a safe supplement, and without an appreciation of the zinc-copper relationship might easily overlook relating these symptoms to zinc supplementation. To avoid an iatrogenic copper deficiency, the study authors give three recommendations: check both C-reactive protein and albumin levels when interpreting plasma zinc concentrations, use daily doses that fall below the upper limit of 45 mg/day, and if prescribing zinc for more than 3 months, monitor plasma copper concentrations. ■

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ABSTRACT & COMMENTARY

Lowering LDL with Ezetimibe

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

Dr. Karpman reports no financial relationships relevant to this field of study.

SYNOPSIS: The addition of ezetimibe to statin therapy in stable patients who had suffered an acute coronary syndrome and who had LDL cholesterol levels already within guideline recommendations further lowers the risk of cardiovascular events.

SOURCE: Cannon CP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;372:2387-2397.

The use of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) has been clearly demonstrated to reduce both low-density lipoprotein (LDL) cholesterol levels and the risk of cardiovascular events in patients with and without cardiovascular disease.[1-4] Because of the residual risk of recurrent cardiovascular events and safety concerns associated with high-dose statin therapy,[5] additional lipid-modifying therapies that would reduce LDL levels in patients who are on maximal statin therapy have been sought.[6,7]

Ezetimibe reduces the absorption of cholesterol from the intestine and, when added to statin drug therapy, has been demonstrated to reduce LDL cholesterol levels by an additional 23% to 24% on average.[8,9] Because of the uncertainty as to whether further lowering of LDL cholesterol levels achieved with the addition of ezetimibe to statin therapy would lead to a benefit in clinical outcomes, representatives from the Thrombolysis in Myocardial Infarction (TIMI) study group and the Duke Clinical Research Institute (DCRI), in collaboration with an international steering committee, organized a large study in patients who receive standard medical and interventional treatment for acute coronary syndromes. Subjects were randomly assigned in a double-blind fashion to receive either simvastatin in a dose of 40 mg once daily or simvastatin/ezetimibe in doses of 40 mg and 10 mg, respectively.[10] The study enrolled a total of 18,144 patients who were randomized at 1147 sites in 39 countries. The baseline characteristics of the patients in the two studies were well matched. Simvastatin increased to 80 mg for elevated LDL cholesterol levels in 27% of patients in the simvastatin-monotherapy group and in 6% of the patients in the simvastatin-ezetimibe group. The results demonstrated that the addition of ezetimibe to statin therapy in stable patients recovering from an acute coronary syndrome and who had LDL cholesterol levels within guideline recommendations further lowered LDL cholesterol levels and the risk of cardiovascular events. No adverse or toxic events were observed.

■ COMMENTARY

The results of the IMPROVE- IT trial in essence demonstrated that the combination of simvastatin and ezetimibe resulted in significantly lower LDL levels and a lower risk of cardiovascular events than occurred in patients who are treated with statin monotherapy.[10] These findings directly support the conclusion that a non-statin lipid-lowering agent can also reduce cardiovascular risk and indirectly support the LDL hypothesis; that is, lowering LDL cholesterol leads to a reduction in cardiovascular events and the benefits occurred because the LDL cholesterol was lowered and not simply because patients were given a statin drug. The same relationship between reduction in LDL cholesterol levels and clinical benefits is seen even when different statins and/or different statin doses are administered.[4] It is quite probable that even greater LDL-lowering benefits from ezetimibe therapy may have been seen if statins had not been initially used. Therefore, baseline LDL levels almost certainly would have been higher.

Other LDL cholesterol-lowering drugs for use with statin drugs are now being tested, such as PCSK9, an injectable drug that in early studies has been extremely effective in reducing LDL to very low levels with improvement in all cardiovascular outcomes. It should be clearly recognized that all patients in the IMPROVE-IT trial had been hospitalized for acute coronary syndrome within the preceding 10 days, and, therefore, the findings in this study cannot be extended to the vast population of patients who require LDL cholesterol-lowering to prevent the onset of symptomatic coronary artery disease. However, it seems logical to assume based on previously published data[1-4] that intensive LDL cholesterol-lowering by any means would be an appropriate form of therapy for primary cardiovascular disease prevention to prevent the onset of symptomatic coronary artery disease, as well as for secondary prevention of cardiovascular disease. ■

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ABSTRACT & COMMENTARY

Can Dietary Intervention Delay the Onset of Alzheimer's Disease?

By Richard S. Isaacson, MD

Associate Professor of Neurology (Education), Weill Cornell Medical College

Dr. Isaacson reports he is a consultant for Accera.

SYNOPSIS: In a prospective study of an elderly population, moderate adherence to the MIND diet was associated with a 53% reduction in the development of Alzheimer's disease.

SOURCE: Morris MC, et al. MIND diet associated with reduced incidence of Alzheimer's disease. *Alzheimers Dement* 2015; Feb 11. On-line at http://dx.doi.org/10.1016/j.jalz.2014.11.009. [Epub ahead of print].

There has been an explosion of recent evidence supporting the potential effect of nutrition on the development of cognitive decline and Alzheimer's disease (AD). Many recent studies have looked into the effect of nutrition on a variety of conditions, such as mild cognitive impairment due to AD and AD dementia, age-related cognitive decline, and vascular cognitive impairment. This research has demonstrated that therapeutic effects of nutrition are not just limited to cognitive function, with improvements across the spectrum of cardiovascular risk reduction, weight loss, and insulin resistance, among many others. Nutritional interventions include two main types of categories: 1) dietary patterns and 2) single or multi-nutrients. A dietary pattern is a specific style of eating, commonly referred to most simply as a diet. The best example of this category is the Mediterranean-style diet, which has the largest volume of dietary pattern research for AD. Other studies have focused instead on an individual nutrient (e.g., the omega-3 fatty acid DHA) or multiple nutrients (e.g., vitamins B12, B6, and folic acid) in combination.

The Mediterranean diet (MeDi) includes plentiful amounts of plant-derived foods and fresh fruit (as the primary source of carbohydrates), olive oil (primary source of fat), fish and lean poultry (primary source of protein, in low to moderate amounts), red meat (in low amounts), low-fat yogurt and milk (in moderate amounts), and wine (in low to moderate amounts). Regular physical activity is also a part of this diet, which is representative of cultural patterns of eating in countries like Italy, Greece, Spain, and Morocco.

In part, because it has been shown to reduce inflammation, oxidative stress, and insulin levels, MeDi has long been known to help reduce the risk of heart disease, and has been associated with a decreased risk of AD as well. By one estimate, MeDi can decrease AD risk by as much as 40% in older patients. The more strictly the patients adhered to the diet, the more dramatically their risk was reduced. Another dietary pattern, called Dietary Approaches to Stop Hypertension (DASH), was shown to improve cognitive function in a group of hypertensive, overweight subjects when combined with exercise. Based on these data, Morris and colleagues from Rush University Medical Center devised the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND), which was initially shown to be more predictive of slower cognitive decline than MeDi or DASH. In the current study, Morris and colleagues aimed to shed more light on the effect of MIND adherence, more specifically on the development of AD rather than cognitive decline alone. The MIND diet is characterized by whole grains (> 28/week), green leafy vegetables (7+/week), berries (½ cup/day), regular cheese (≤ 1/day), butter (< 1 T/day), beans (3+/week), nuts (1/8 cup/day), lean red meats (< 4/

week), fish (1+/week), poultry (2+/week), olive oil (> 1 T/d), and alcohol/wine (> 1/day). Key differentiating factors from MeDi and DASH include fewer grains/week, an emphasis on whole grains and berries, more red meat (but lean), less olive oil than MeDi, and unlike DASH, no specific percentage of total fat/saturated fat.

This study prospectively followed more than 900 people aged 58-98 years over 4.5 years and asked them to track their food patterns via food frequency questionnaires. Morris and colleagues found that moderate adherence to the MIND diet was associated with a 53% reduced risk of AD for those in the highest tertile of adherence (compared to a 35% risk reduction in the middle tertile). This effect was independent of other lifestyle conditions and cardiovascular-related conditions. When compared to adherence to MeDi and DASH, only those with the highest adherence to these dietary patterns showed an association with AD prevention.

■ COMMENTARY

To reinforce these associations, two recent randomized, controlled trials (RCTs) have found additional support for the importance of nutritional interventions for AD. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study[1] was the first longitudinal RCT to prove that multimodal lifestyle intervention (nutrition, exercise, cognitive training) reduces the risk of cognitive decline. The second RCT by Ros and colleagues[2] randomized subjects to three groups. Two of the groups followed the MeDi, also adding either 5 tablespoons of extra virgin olive oil each day or a handful of mixed nuts (30 grams of almonds, walnuts, or hazelnuts) each day. The third group followed a low-fat diet. Compared to the low-fat diet group, cognitive function in the areas of attention and executive function were higher in the MeDi plus olive oil group, and memory function was higher in the MeDi plus nuts group. Although further RCTs are warranted, from a practical clinical perspective, targeted nutritional interventions are an evidence-based and safe means of reducing the risk of AD and cognitive decline. ■

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PHARMACOLOGY UPDATE

Isavuconazonium Sulfate Capsules and Injection (Cresemba®)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved a new antifungal agent for the treatment of serious fungal infections. Isavuconazonium sulfate is designated as a Qualified Infectious Disease Product (QDIP), a designation given to drugs to treat serious or life-threatening infections. Isavuconazonium is an azole antifungal and the prodrug of isavuconazole. It was also given an orphan status for rare fungal infections. It is marketed by Astellas Pharma US, Inc. as Cresemba.

INDICATIONS

Isavuconazole is indicated for the treatment of invasive aspergillosis and invasive mucormycosis.[1]

DOSAGE

The recommended dose is 372 mg intravenously or orally every 8 hours for 6 doses and once daily thereafter. Isavuconazonium sulfate is available as 372 mg (equivalent to 200 mg of isavuconazole) single dose vials or 186 mg of isavuconazonium sulfate (equivalent to 100 mg of isavuconazole) capsules.

POTENTIAL ADVANTAGES

Isavuconazole provides an alternative for the treatment of invasive aspergillosis and mucormycosis. The prodrug is water soluble and in contrast to voriconazole does not require the solubilizing agent sulfobutyl ether-ß-cyclodextrin (SBECD) — an excipient that accumulates in patients with moderate to severe renal insufficiency. The oral formulation is recommenced for this population.[2]

POTENTIAL DISADVANTAGES

Cases of severe liver adverse events (hepatitis, cholestasis or hepatic failure, including death) have been reported in patients with serious underlying medical conditions such as hematologic malignancy.[1] Isavuconazole is a substrate for CYP3A4 as well as a moderate inhibitor of CYP3A4; therefore, its levels may be altered by

Isavuconazonium is an azole antifungal and the prodrug of isavuconazole..

CYP3A4 inhibitors and inducers. Infusion-related reactions have been reported.[1] Common adverse events, including gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea), peripheral edema, and headache, were similar to that reported for voriconazole.[1] Isavuconazole may be less active in vitro against *Aspergillus spp*. than voriconazole.[3]

COMMENTS

The approval of isavuconazole was based on two studies. Trial 1 was a randomized, double-blind, non-inferiority active controlled trial comparing isavuconazole to voriconazole in participants with proven, probable, or possible invasive aspergillosis. The second was an open-label noncomparative trial in participants with proven or probable invasive mucormycosis.[1] In trial 1, participants generally had hematologic malignancies (84%) with a high percentage of neutropenia (65%). Participants (n = 516) were randomized to isavuconazole (200 mg IV every 8 hours for 48 hours, then 200 mg once IV or orally daily) or voriconazole (6 mg/kg IV every 12 hours for the first 24 hours, 4 mg/kg IV every 12 hours for the next 24 hours, then 200 mg orally every 12 hours). The maximum duration was 84 days (mean 47 days). The efficacy endpoint was all-cause mortality through day 42 and overall response success at end-of-treatment (EOT), last day of drug administration. Overall, success was assessed by a blinded committee based on predetermined clinical, mycological, and radiological responses. The rates for all-cause mortality were 18.6% for isavuconazole and 20.2% for voriconazole for a difference of -1.6% (95% confidence interval, -8.0 to 5.9). EOT rates were 35% compared to 38.9% for voriconazole. In the open-label trial in participants with invasive mucormycosis, all-cause mortality was 38% and EOT success was 31%.

CLINICAL IMPLICATIONS

Isavuconazole provides an alternative for the treatment of invasive aspergillosis and mucormycosis. Currently, voriconazole is the treatment of choice for invasive aspergillosis and liposomal amphotericin or amphotericin lipid complex is treatment of choice for mucormycosis.[4,5] The wholesale cost for an oral one-week maintenance dose of isavuconazole is $1960. ■

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Clinical Briefs

By Louis Kuritzky, MD

Beta-blocker, Shmeta-blocker…Or Are There Important Differences?

SOURCE: Aparicio LS, et al. Comparison of atenolol vs bisoprolol with noninvasive hemodynamic and pulse wave assessment. J Am Soc Hypertens 2015;9:390-396.

Aside from beta-receptor selectivity (beta-1 receptors being involved in cardiac function, beta-2 in pulmonary function), clinicians do not often distinguish major differences within the class of beta-blockers. Alpha-beta-blockers (e.g., carvedilol, labetalol) are not really beta-blockers in the traditional sense because they also provide alpha-receptor blockade. And then there is nebivolol, the nitric-oxide-enhancing beta-blocker associated with — in contrast to most other beta-blockers — peripheral vasodilation. Traditional beta-blockers are associated with peripheral vasoconstriction, which may result in complaints of cold extremities. In 2006, it was brought to the attention of clinicians that while various drugs may lower BP equivalently, they may not always reduce CV endpoints to the same degree. In the ASCOT trial, which compared amlodipine to atenolol, CV outcomes were more favorable with amlodipine, despite similar BP results. The CAFÉ trial (Conduit Artery Function Evaluation) determined that even though arm BP (sometimes called peripheral BP) was similar with either drug (amlodipine or atenolol), central BP (measured at the level of the aorta) was lowered substantially better with amlodipine. Such differences might explain the advantageous outcomes in favor of amlodipine. Aparicio et al compared central BP effects of bisoprolol and atenolol, and found them to be comparable. Whether clinicians should choose pharmacotherapy based upon central BP effects has not been confirmed, although hypertension guidelines throughout the world have increasingly recognized the inadequacy of traditional beta-blockers in comparison to most other classes of agents and relegated them to a lower position on the therapeutic ladder. ■

Delay in Diagnosis of Hepatocellular Carcinoma

SOURCE: Patel N, et al. Diagnostic delays are common among patients with hepatocellular carcinoma. *J Natl Compr Canc Netw* 2015;13:543-549.

Hepatocellular carcinoma (HCC) is the third-leading cause of cancer mortality worldwide. It is increasing in the United States, paralleling the rise in non-alcoholic fatty liver disease and hepatitis C. When diagnosed early, the 5-year survival rate is as high as 70%, but diminishes to less than 1 year when diagnosed at an advanced stage. Cirrhosis patients have been suggested to undergo ultrasound screening twice yearly, but not only does this process have only modest sensitivity (32%) it is often not followed by clinicians (or patients). Since 40% of HCC cases present with no previously recognized signs of liver disease, it becomes easier to understand how cases go "under the radar." Patel et al studied cases of HCC (n = 457) that presented to a large hospital and its affiliated primary care clinics in Dallas between 2005 and 2012. Almost half of the patients had received the HCC diagnosis as inpatients, which was associated with a very short lag time between presentation and diagnosis (< 1 week). For those diagnosed as outpatients (n = 226), the delay from presentation to diagnosis was substantial. For instance, almost 40% of HCC diagnosed among outpatients incurred a 3-month delay from time of presentation, an interval which has been associated with meaningful disease progression. Healthcare sites that employed electronic medical records showed fewer diagnostic delays. There was also a patient-dependent role in diagnostic delay, wherein some patients did not follow up recommended return visits, an occurrence more common among patients with hepatic encephalopathy. The authors encourage timely identification and follow up of persons at-risk for HCC. ■

Initial Orthostatic Hypotension: An Under-recognized Form of Orthostatic Hypotension

SOURCE: McJunkin B, et al. Detecting initial orthostatic hypotension: A novel approach. J Am Soc Hypertens 2015;9:365-369.

Orthostatic hypotension (OH) is typically defined as a decline in BP > 20/10 mmHg within 3 minutes of standing. OH is consequential not only because of adverse symptoms such as dizziness, blurred vision, or so-called "coat-hanger" headache, but also because it is associated with falls. Fall risk leads to life-changing consequences such as hip fractures and the loss of autonomy due to non-independent living.

A less familiar form of orthostasis is termed initial orthostatic hypotension (IOH). IOH is characterized by a dramatic decline in BP (> 40/20 mmHg) presenting within the first 15 seconds of standing, which self corrects within 30-60 seconds. IOH differs from the normal physiologic experience many of us have had during a transient decrease in BP that recovers by 30 seconds. IOH is a prolongation of recovery time during which patients might experience hypotensive symptoms, or even falls. One of the limitations of prior investigations about IOH has been the delay in BP measurement incurred by simply using 5-10 seconds or more to inflate the BP cuff to measure the BP in the first place. McJunkin et al suggest this obstacle can be obviated by fully inflating the cuff while a patient is supine, allowing immediate deflation and BP measurement upon standing. Among a population of elderly patients (n = 115) 12% were found to have OH, and 3.5% to have IOH. IOH represents a population at risk for falls which may be missed with "traditional" methods of orthostatic BP measurement. ■

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CME QUESTIONS

1. Zinc supplementation in large does is connected to:

a. potassium deficiency.

b. hypernatremia.

c. hypophosphatemia.

d. copper deficiency.

2. The addition of ezetimibe to statin therapy in patients who had suffered an acute coronary syndrome and who already had LDL levels within guideline recommendations:

a. had no effect upon the LDL levels.

b. lowered the risk of cardiovascular events.

c. had no effect upon the risk of cardiovascular events.

d. was not well tolerated.

3. Which of the following dietary patterns has not been associated with delay of cognitive and/or Alzheimer's disease?

a. Dietary Approaches to Stop Hypertension (DASH)

b. Mediterranean diet (MeDi)

c. Vegan diet

d. Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND)

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

[IN FUTURE ISSUES]

Long-term weight loss rivals medications and ablation for atrial fibrillation rhythm control

Inferior vena cava filters and recurrent pulmonary embolism