

Therapeutics & Toxins News

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“As the amount of dietary copper increases, absorption decreases and this balance is regulated by an active transport system at low dietary levels “

The Good, the Bad and the Toxic Side of Elements, Part II: Copper

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As a continuation from the last issue, the focus of this article is the second of the nutritional but potentially toxic elements. As mentioned last time, it is element 29 (copper) and is widely used in handrails and doorknobs to reduce the spread of pathogens and serves as another reminder that too much of a good thing can sometimes be bad.

Background

Absorption

Copper is predominately absorbed in the small intestine with minimal absorption occurring in the stomach. As the amount of dietary copper increases, absorption decreases and this balance is regulated by an active transport system at low dietary levels (mediated by solute carrier family 3 transporters (1)) with passive diffusion occurring at high dietary levels (2). Copper absorption is reduced in the presence of elevated zinc as a result of metallothionein induction and this relationship forms the basis for oral zinc therapy in genetic copper imbalance (3).

Distribution

Copper is shuttled by chaperone proteins intracellularly with efflux into circulation regulated by P-type transport ATPases (4). Once in circulation, copper is transported to the liver bound to albumin with the majority of copper leaving the liver bound to ceruloplasmin. Surprisingly, the genetic disease aceruloplasminemia does not severely disrupt copper metabolism but does result in iron overload, indicating that other compensatory mechanisms of copper transport exist (5).

Excretion

In normal physiology, excess copper that reaches the liver is exported into the bile while a minor amount is excreted renally. (continue on page 2)



Logo for Therapeutic and Toxin Newsletter

The Good, the Bad and the Toxic Side of Elements, Part II: Copper (continued from page 1)

In copper overload, tubular reabsorption is exceeded and urine copper levels are considerably elevated (2). The half-life of copper in normal individuals is on the order of several weeks (2, 6).

Pathophysiology of Overload

Acute Toxicity:

The clinical presentation and underlying mechanism in copper toxicity is similar to that of iron overload (4). Gastrointestinal disturbances including nausea, vomiting and diarrhea are commonly seen in acute ingestion.

Symptoms

Acute toxicity is characterized by corrosive injury to the upper gastrointestinal system producing the gastrointestinal disturbances noted above. Acute renal failure due to copper itself or due to hemolysis observed with elevated copper in the blood has been noted in severe cases (7). Inhalation of copper fume may result in metal fume fever characterized as an influenza-like syndrome within a few hours of exposure and lasting up to several days (2).

Causes

Intentional ingestion of a toxic dose of copper sulfate has been used to commit suicide. Unintentional copper toxicity has been reported after its use as an emetic and after ingestion of large quantities of coins (7). Exposure to copper fume can occur during welding or refining processes (6).

Treatments

Treatment of acute copper toxicity is largely supportive based upon symptoms with relatively little guidance available regarding the use of the available chelating agents (7). The overall treatment plan primarily includes fluid and electrolyte replacement with chelation therapy utilized in severe ingestions (8).

Chronic Toxicity:

Chronic copper toxicity is uncommon in individuals capable of maintaining a normal copper balance. In patients with Wilson disease, malfunctions in the copper-transporting P-type ATPase ATP7B caused by mutations in the *ATP7B* gene lead to the accumulation of copper in various tissues. Symptoms are highly variable in their presentation and age of onset. Hepatic and neurologic forms have been described with the majority of patients presenting with a mixture of both. Regardless, the onset of hepatic abnormalities typically precedes neurologic dysfunction (3).

Symptoms

The onset of Wilson disease is typically between the ages of 3 and 40 years; however, it has been reported that about 4% of patients present after 40 years of age (9). Hepatic symptoms may include elevated enzymes, liver enlargement and in severe cases chronic liver failure. Neurologic abnormalities may include motor dysfunction and psychiatric symptoms (3). (continued on page 3)

“For acute toxicity, the clinical presentation includes: Gastrointestinal disturbances including nausea, vomiting and diarrhea.”

Copper (continued from page 2)

Granular deposits in the cornea cause the hallmark Kayser-Fleischer ring in the neurologic form of Wilson disease but may be present in up to 60% of patients without neurologic symptoms (10).

Treatments

Life-long drug therapy is the mainstay for individuals diagnosed with Wilson disease and includes the use of copper chelators such as D-penicillamine or oral zinc administration. Following initial chelation therapy to remove excess copper from the blood, low dose chelation or ingestion of zinc salts is required regardless of the reduction in symptoms (3, 8).

Lab Testing for Toxicity

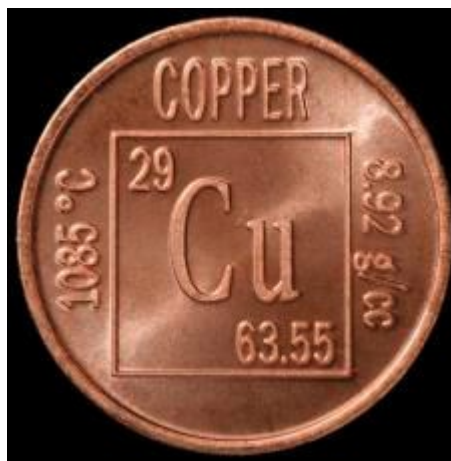
Acute:

Acute copper overload is largely a clinical diagnosis, but laboratory testing can be used to determine severity and success of treatment. Elevations of serum copper have been described in severe ingestions while urine copper levels are of limited utility (2, 7).

Chronic:

Laboratory results from patients presenting with symptoms consistent with Wilson disease typically include low serum ceruloplasmin, elevated urinary copper excretion and liver function abnormalities. Though not always required for diagnosis, copper concentration in a liver biopsy from a patient with Wilson disease will most often exceed 250 $\mu\text{g/g}$ (3). Two recent guidelines are available that discuss diagnostic strategies for Wilson disease (11, 12). Both highlight the calculation of non-ceruloplasmin bound copper using concentrations of serum copper and serum ceruloplasmin as potentially useful; however, both list concerns over the performance of necessary methods and the potential for overestimation of ceruloplasmin saturation. Clinical methods for the direct measure of non-ceruloplasmin bound copper are available (13) but discussion of their utility in current guidelines is absent. In addition, alternative assessments of copper status such as relative, exchangeable copper (14) are of unknown utility.

“Laboratory results from patients presenting with symptoms consistent with Wilson disease typically include low serum ceruloplasmin, elevated urinary copper excretion and liver function abnormalities.”



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Copper (continued from page 3)

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"Acute copper overload is largely a clinical diagnosis, but laboratory testing can be used to determine severity and success of treatment."



Highlight of Events at AACC for TDM/Tox Division

SHORT COURSES— Related to TDM/TOXICOLOGY

191001—Advanced Applications of Molecular Diagnostics and Pharmacogenomics in Targeted Therapeutics

Sunday, July 28th; 10:30–12 noon; 1:30-4:00pm

191003—Resolving Erroneous Results in Therapeutic Drug Monitoring and Toxicology

Sunday, July 28th; 10:30–12 noon; 1:30-4:00pm

73107—How to Clean-Up Body Fluids for LC-MS/MS Analysis of Small Molecules
Tuesday, July 30th; 10:30-12 noon

73122—A Laboratorians' Guide to Performing Urine Drug Testing and Pharmacogenomics for Pain Management

Tuesday, July 30th; 10:30-12 noon

73215—Troubleshooting LC-MS/MS in the Clinical Laboratory

Tuesday, July 30th; 2:30-5:00pm

73217—Designer Drugs and Mass Spectrometry: The Tug-o-War Between Thugs and Labs

Tuesday, July 30th; 2:30-5:00pm

74106—Alcohol Biomarkers: Biochemical and Genetic Markers for Alcohol Intake and Abuse

Wednesday, July 31st; 10:30-12 noon

SYMPOSIAS

32103—Sports Drug Testing and Forensic Toxicology Laboratories: Twins Separated at Birth or Just Distant Relatives?

Monday, July 29th; 10:30–12:00 noon

32216—Hot Topics in Therapeutic Drug Management

Monday, July 29th; 2:30-5:00pm

32227—Forensic Applications of Mass Spectrometry and Next Generation Sequencing

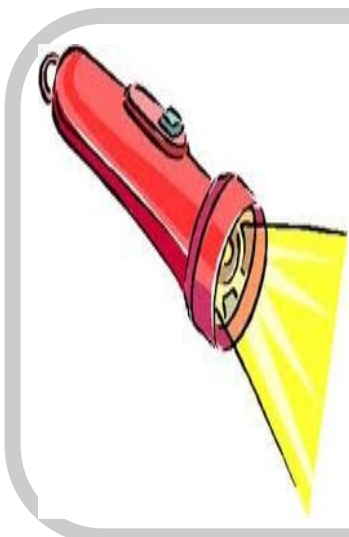
Monday, July 29th; 2:30-5:00pm

33101—Oral Fluid as an Alternate Specimen for Workplace, Clinical and Forensic Toxicology

Tuesday, July 30th; 10:30am-12 noon

33211—Chemotherapy and Drug Management

Tuesday, July 30th; 2:30-5:00pm



Highlight of Events at AACC for TDM/Tox Division

ROUNDTABLES

42113/52213—Taking the Pain out of Pain Management
Monday, July 29th; 7:30-8:30am or 12:30-1:30pm

43109/53209—Role of Therapeutic Drug Monitoring in Pediatric Cancer
Chemotherapy
Tuesday, July 30th; 7:30-8:30am or 12:30-1:30pm

43117/53217—Prescription Drug Compliance Monitoring Decision Support for
Test Ordering and Result Interpretation
Tuesday, July 30th; 7:30-8:30am or 12:30-1:30pm

43122/53222—Chronic Cadmium Toxicity: What Laboratorians Need to Know
Tuesday, July 30th; 7:30-8:30am or 12:30-1:30pm

43123/53223—What's in a Number? Advantages of Qualitative Screening of Pain
Management Medications and Drugs of Abuse by LC-MS/MS
Tuesday, July 30th; 7:30-8:30am or 12:30-1:30pm

43129/53229—Drug Abuse Among Children and Adolescents: Beyond Traditional
Drugs of Abuse
Tuesday, July 30th; 7:30-8:30am or 12:30-1:30pm

44106/54206—How People Try to Beat Drug Testing and Defend Positive Results
Wednesday, July 31st, 7:30-8:30am; 12:30-1:30pm

44109/54209—Urine Testing for Opiate Use and Abuse
Wednesday, July 31st, 7:30-8:30am; 12:30-1:30pm

44113/54213—Serum Drugs of Abuse Testing Using Liquid Chromatography-Time-
of-Flight Mass Spectrometry TOF LC-MS
Wednesday, July 31st, 7:30-8:30am; 12:30-1:30pm

44114/54214—Issues in Providing a Regional Toxicology Service
Wednesday, July 31st, 7:30-8:30am; 12:30-1:30pm

44122/54222—Selecting and Implementing Your First LC-MS/MS System—
Practical Tips for the Novice
Wednesday, July 31st, 7:30-8:30am; 12:30-1:30pm

*“Don't forget to check out
the Poster Sessions that
pertain to TDM and Toxi-
cology at AACC”*



UPCOMING MEETINGS OF INTEREST

AMERICAN ASSOCIATION FOR CLINICAL CHEMISTRY (AACC)

Annual Meeting

July 28–August 1, 2013, Houston TX.

www.aacc.org

CSCC TOXICOLOGY INTEREST GROUP MEETING

AACC Annual Meeting

July 29, 2013, Time : 7:30am–9am

Hyatt Regency

TDM & TOXICOLOGY DIVISION MEETING & LUNCHEON

AACC Annual Meeting

July 29, 2013, Time : 12noon–2pm

Hilton Americas

THE INTERNATIONAL ASSOCIATION OF FORENSIC TOXICOLOGISTS (TIAFT)

Annual Meeting

September 2–6, 2013, Madeira, Portugal

www.tiaft.org

INTERNATIONAL CONGRESS OF THERAPEUTIC DRUG MONITORING & CLINICAL TOXICOLOGY (IATDMCT)

September 21-26, 2013, Grand America Hotel, Salt Lake City, UT.

www.iatdmct.org

THE AMERICAN ACADEMY OF CLINICAL TOXICOLOGY

North American Congress of Clinical Toxicology (NACCT)

September 27–October 2, 2013, Hyatt Regency Atlanta, GA.

www.clintox.org

SOCIETY OF FORENSIC TOXICOLOGISTS (SOFT)

Annual Meeting

October 28–November 1, 2013, Orlando, FL.

www.soft-tox.org

*“TDM/Tox Division
lunch meeting will be
held on July 29th from
12-2pm at the Hilton
Americas.”*



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DRUGS IN THE NEWS

This is an official **CDC HEALTH ADVISORY**



Distributed via the CDC Health Alert Network
June 20, 2013, 15:15 ET (3:15 PM ET)
CDCHAN-00350

Recommendations for Laboratory Testing for Acetyl Fentanyl and Patient Evaluation and Treatment for Overdose with Synthetic Opioids

Summary: *Recently, a number of intravenous drug users have overdosed on a new, non-prescription injected synthetic opioid, acetyl fentanyl. Acetyl fentanyl is a fentanyl analog previously undocumented in illicit drug use that is up to five times more potent than heroin. CDC recommends increased vigilance by public health agencies, emergency departments, state laboratories, medical examiners, and coroners for patients with symptoms consistent with opioid overdose and laboratory results showing an enzyme-linked immunosorbent assay (ELISA) positive for fentanyl. CDC also recommends that public health officials work with laboratories to carry out ELISA screens for fentanyl, and if the results of these screens are positive for fentanyl, conduct gas chromatography-mass spectrometry (GC/MS) confirmatory testing on specimens to confirm or rule out fentanyl and its analogs, including acetyl fentanyl.*

<http://www.emergency.cdc.gov/HAN/han00350.asp>

Please contact Dr. Kamisha Johnson-Davis at kamisha.johnson-davis@aruplab.com if you are interested in joining the editorial board or if you have ideas or article contributions for this newsletter.