

AACTion

Volume 19, Number 4
April 2009

American
Academy
of Clinical
Toxicology,
Inc.



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President's Corner Michael I. Greenberg, MD, MPH, FAACT



Spring's Re-birth

Spring represents a re-birth for all things; or so they say. So while I'm in a springtime mood (its 75 degrees today in Philly!!!) I'd like to tell you about what I see as a re-birth initiative for AACT as well as a new birth initiative for AACT.

In the "re-birth" category I am pleased to report that after considerable thoughtful deliberations the AACT Fellow Committee (Donna Seger, Rob Palmer, Maria Mercurio-Zappala, Tony Scalzo, and Mike Holland), chaired by Ruddy Rose, has revised and updated the guidelines that direct the requirements for an AACT member to apply for designation of FAACT status. Of course, the elevation to FAACT status is an important landmark in the career of any clinical toxicologist as it represents recognition by peers of the highest level of achievement in academic productivity and service to both AACT and the specialty of clinical toxicology. I encourage all AACT members to go to the new website at www.clintox.org and download the guidance document for FAACT and carefully review it. If, after review of the requirements, you are interested in applying for FAACT status, please follow the directions outlined in the application form (also available for download on the website). I am looking forward to seeing many deserving members apply for, and achieve, FAACT status this year and in years to come.

In the "new birth" category I am excited to announce that AACT will be sponsoring a new and different type of Medical Review Officer (MRO) course at the upcoming NACCT '09 in San Antonio in September. We are calling this course offering "MRO-PLUS: Medical Review Officer Training PLUS Forensic Toxicology for the Clinical Toxicologist". The "MRO" content of the course will be a full MRO course, the completion of which will qualify physician participants to take the MRO certifying exam (the exam is an on-line or take at home test, offered by two other organizations). The "PLUS" part of the course is an exciting addendum that supplements MRO training wherein we will be addressing a number of important issues in Forensic Toxicology. "MRO-PLUS" will cover the most important aspects of forensic drug and alcohol testing and interpretation of forensic drug tests, as well as such topics as post-mortem drug testing, post mortem redistribution phenomena, alcohol (ETOH) issues including driving and working under the influence of alcohol, driving and working under the influence of marijuana and a variety of interesting and instructive case scenarios in Forensic Toxicology.

"MRO-Plus" is poised to become the premiere course in Forensic Toxicology for clinical toxicologists and I look forward to seeing as many of you as possible at the course. Registration materials for "MRO-PLUS" will be included with NACCT registration materials to be sent out in just a few weeks.

Save the Date: The 2009 NACCT Meeting in San Antonio, TX will be held September 21- 26. A post-symposium MRO PLUS course on September 26 & 27, 2009 immediately follows NACCT 2009, and will satisfy the US DOT pre-requisites for certification as an MRO for workplace drug testing reviews, as well as expanding on necessary forensic testing and interpretation.

AACTion

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Website Update: Special Interest Groups, *Clin Tox* Access

Michael G. Holland, MD



AACT's newly re-designed website has many new features. We hope members have had a chance to view them and to become more familiar with the new site. One great feature is a more prominent place for

viewing Special Interest Groups' activities. Each SIG has its own drop-down link right on the homepage, which connects to their content page; the page can be as detailed as the group would like. Many SIGs use their page to attract new members, update the Academy about their current activities, and advertise upcoming educational events sponsored by their SIG.

In addition, the SIG page contains email addresses of group leaders, and can even be used as a forum for disseminating new articles of interest to the members. Some SIGs keep an archive of their past activities on their page as well. The SIG page is the forum for the SIGs: it is their voice to the toxicology world. The Academy encourages all SIG leaders to regularly update their pages with news of their activities.

One of our most valuable member benefits is the subscription to our scientific journal, *Clinical Toxicology*. The journal is available in on-line version through our website via a direct link to InformaWorld, the publisher of the journal. Members have always enjoyed access to full text content through our website link. However, due to platform changes at Informa and our website redesign, there have recently been glitches in the system. After launching of the new website, some users found their full text access was denied, and were directed to the pay-per-article page. Through much diligent work between the

publisher and our web designer, the problems appear to be fixed. However, a separate and unrelated incident is that while we all should have full content access through the members-only link on the site, the green icon that used to show up indicating you have full access no longer appears. This is an error from the publisher's site, which they are working on. Despite not displaying the small green full-access icon, members do indeed have full access through this site. When you click on the article you want, the full text pops right up (I recommend you right-click on the link of the individual article, and scroll down to the choice "open in new window"- that way you won't navigate away and can access multiple articles if needed).

For those who had experienced some problem accessing the full text last week, the problem should be solved now. If you are still experiencing access denied messages, it may be due to your computer storing the incorrect "cookie" from the previous problem period. The publisher's representative for our journal access, Phil Garner, advises that anyone who is still experiencing problems should go to "tools" menu on your browser page, scroll to internet options, then delete the browsing history, cookies, and passwords. This should reset your cache. Phil informed the Academy that since fixing the links, AACT members are using the *Clin Tox* access via the referral link, and are getting access to the full content.

Please continue to visit the AACT website for updated information regarding Academy activities, and new features as we roll them out. And please contact me with any questions, suggestions, problems, or how we can make it better for you. This is your website, and we want it to be a valued member benefit.

Archives of the Drug Information Service at Upstate Poison Center SUNY Upstate Medical University; Syracuse, NY

Jamie Nelsen, Pharm.D. DABAT



Question: What is the significance of an elevated serum potassium concentration in a patient with chronic digoxin poisoning? Does the presence of renal failure make a difference?

Answer:

Digoxin is a cardiac glycoside that is commonly prescribed to patients with heart failure and/ or atrial fibrillation; it is cleared primarily via renal elimination. Digoxin has two primary mechanisms: 1) it stimulates the vagus nerve to release acetylcholine, thereby producing bradycardia via augmentation of the parasympathetic nervous system, and: 2) most importantly, it inhibits the sodium-potassium-ATPase transport pump, thereby increasing the intracellular sodium concentration, which inhibits calcium extrusion from the cell, resulting in increased inotropy (cardiac cell contraction).^{1,2} It is this latter mechanism that may result in an elevated serum potassium concentration in the presence of digoxin.

Hyperkalemia has traditionally been recognized as a poor prognostic indicator in the setting of acute digoxin toxicity.³ Bismuth et. al initially evaluated the relationship between serum potassium levels and mortality in 91 patients with digitoxin poisoning, 89% of whom had acute toxicity. It was observed that no patient whose initial serum potassium level was > 5.5 mEq/L survived (study was pre-dig Fab availability), and no patient with a level < 5.0 died. The value of serum potassium levels in the setting of chronic digoxin toxicity, which was not teased out in the study, remained difficult to ascertain. Additionally, the authors had excluded patients with disease states likely to raise potassium concentrations, including oliguria, making it difficult to extrapolate the prognostic value of hyperkalemia in these patients.

Recently two studies have shed some light on the prognostic value of serum potassium level in chronic dig glycoside intoxications. Lapostolle et al. performed a retrospective review of digoxin (91%) and digitoxin (9%) poisoned patients, of which 86% had chronic toxicity.³ When serum potassium concentration exceeded 4.5 mEq/L, it was found to be a significant prognostic factor for death regardless of renal function or acute versus

chronic toxicity.

Levine et al. similarly performed a retrospective study in digoxin-poisoned patients, of which 99% had chronic digoxin toxicity. The primary goal of this study was to assess the safety of intravenous calcium administration in the setting of hyperkalemia and digoxin toxicity; therefore, although they also assessed the relationship between serum potassium and mortality, the study wasn't powered to statistically evaluate the relationship. Renal impairment was significant in this population and the mean serum creatinine concentration was 2.72 mg/dL.² A multivariate logistic regression analysis was performed evaluating the relationship between mortality and several clinical variables including creatinine, age, serum potassium level, calcium administration and digoxin concentration. The authors reported that peak potassium concentration (≥ 5.5 mEq/L) showed a trend towards increased mortality, with an odds ratio for death of 2.0. However, this was not statistically significant ($p=0.07$, 95% CI 0.93- 4.5). Again, this may be because of inadequate power to detect such differences, but it poses an interesting question and highlights concerns that were raised in the Lapostolle study, which found that despite elevated potassium concentrations in the chronic toxicity group, these patients were less likely than acutely poisoned patients to receive antidotal therapy.¹

In conclusion, hyperkalemia may be a valuable prognostic marker for increased risk of mortality in chronic as well as acutely poisoned digoxin patients and may be considered an indication for digoxin-specific antibody fragments.

1. Lapostolle F, Borron SW. Digitalis: In Haddad & Winchester's Clinical Management of Poisoning and Drug Overdose. Eds: Shannon M, Borron SW, Burns M. 4th edition, 2007.
2. Levine M, et al. The Effects of Intravenous Calcium in Patients with Digoxin Toxicity. J Emerg Med 2009. *In Press, Corrected Proof*, Available online 6 February 2009.
3. Bismuth C, et al. Hyperkalemia in Acute Digitalis Poisoning: Prognostic Significance and Therapeutic Implications. Clin Tox 1973;6(2):153-62.
4. Lapostolle F, et al. Assessment of Digoxin Antibody Use in Patients with Elevated Serum Digoxin Following Chronic or Acute Exposure. Intensive Care Med 2008; 36(11): 3014-18.

Selected Cases from *Merck's Archives of Materia Medica and Drug Therapy, 1901*

Michael Hodgman, MD



Poisoning by Lysol

A 14 yo boy was given a rectal injection of 1.5 oz Lysol in a pint water as treatment for dysentery. One half hour later he was unconscious and 4 hours later, when examined by a physician "was in a state of complete collapse, sweating profusely, with legs drawn up, and with pinhole pupils; and the

respiration forty per minute; the pulse was almost uncountable, and the temperature subnormal" (1). Strychnine and ether were administered parenterally. Shortly later "dark-brown grumous blood was suddenly ejected from mouth and nose, and exitus lethalis took place."

The original Lysol products were a mix of coal tar cresols and soap. Cresols are a mixture of the three isomers of methyl phenol. A 1937 text from the Medical Examiner's Office of New York City reported that poisoning by Lysol was indistinguishable from that of phenol, and that the presence of cresols and fatty acids must be documented if Lysol is suspected (2). (In 1935 the Office of the Chief Medical Examiner of New York City reported 25 cases of Lysol poisoning and 4 cases of phenol out of 15,557 deaths examined).

Cresols are powerful irritants. In addition to local injury to skin and mucosal surfaces, systemic effects include hemolysis, methemoglobinemia, hypotension, ventricular arrhythmias, pulmonary edema and hepatic and renal necrosis (3). This teenager appears to have experienced massive hemolysis, shock and pulmonary edema.

Poisoning by Vapo-Cresolene

Cresols were used for other maladies in the late 19th and early 20th century. Vapo-Cresolene was marketed as a remedy for a variety of respiratory problems. Another article in the Jan. 1901 *Merck's Archive*, excerpted from 1900 *Transactions of the American Pediatric Society of Pediatrics*, describes 2 children treated with Vapo-Cresolene for respiratory illnesses who developed systemic toxicity.

The first was an infant of 6 months who had been breathing Vapo-Cresolene fumes for 24 hours. The child was found by the physician to be "in coma, and in a cold, clammy sweat. There was marked pulmonary edema." By then the child was anuric but

had passed "black urine" earlier. Treatment with fresh air and water led to recovery.

In the second case a 6 month old was found with stridor, rales, diaphoresis and a low grade fever. The child had slept the night before with a Vapo-Cresolene lamp at bedside. The physician reports a strong odor of carbolic acid (phenol). This child improved with fresh air and water. "Smokey urine" was not observed in this case (4).

The similarity to phenol is such that even the fumes were similar to those of carbolic acid. We can presume the first child had both pulmonary injury and hemolysis while the second child had not been as severely poisoned.

In the early 1900's The American Medical Association published several books on fraudulent medications and therapies. The second edition of *Nostrums and Quackery* concluded that Vapo-Cresolene was a hazard and inherent in this product were the "dangers attendant on the inhalation of any of the phenols" (5).

Phosphorous poisoning

An intoxicated male drank a quantity of a phosphorous containing rodenticide. He immediately developed severe abdominal pain and vomiting, treated with salt and hot water. He remained ill and 4 days later was evaluated by a physician. At that time he had intense thirst, repeated emesis and severe abdominal pain. The emesis consisted "wholly of altered blood" (coffee ground?) and stools were "dark and pitchy". He died one-week post ingestion, with repeated hematemesis up until death, despite treatment not described.

The autopsy report was peculiar. The patient appeared icteric but with the skin of the neck appearing to have been stained with Prussian Blue, the "colour being most intense and brilliant". The superficial veins of the extremities were also blue as if "injected with a solution of Prussian blue paint and were most beautifully mapped out". The viscera were also described as deeply pigmented blue with omental hemorrhage and fatty degeneration of heart, liver and kidneys.

White phosphorous has been used as a rodenticide, and if the history is accurate and correct this is likely the form of phosphorous that he

(continued on page 5)

**Merck's Archives of Materia Medica and Drug Therapy, 1901
(Continued from page 4))**

ingested. Phosphorus is caustic to skin and mucus membranes. Early findings with ingestion include nausea, vomiting, abdominal pain and gastrointestinal bleeding. Emesis and stools may have a garlic odor, and a classic trivia fact with ingestion of white phosphorus is smoking stools that may also phosphoresce.

Early cardiovascular collapse may be a result of shock or more direct effects on cardiac contractility or conduction. Hypocalcemia may contribute to cardiac toxicity.

The liver takes up a large portion of ingested phosphorus. Hepatic effects include mitochondrial swelling, steatosis and zone 1 necrosis. CNS toxicity includes irritability, agitation, lethargy, hallucinations, seizures and coma. Renal injury may also occur.

In the early 20th century rodenticides contained 1-4% white phosphorus. Common accidental poisonings from phosphorus in children included ingestion of lucifer matches, the contents of fireworks or rat poison. Alcoholics mistook rat paste for food (2). (Lucifer match was a common name for friction matches that would ignite with friction against any surface. White phosphorus was a component of many friction matches. White phosphorus was used in the past in fireworks as well).

This patient's clinical course follows a biphasic course as is described with phosphorus ingestion, if one survives the acute phase (6). Initial violent illness, then a brief period during which, although not well, he apparently was doing better, and then he becomes more ill. A physician is contacted on day 4 and from there, a progressive decline with death at 1 week post-ingestion.

The pathologic findings reported from phosphorus ingestion include a yellow, enlarged liver, grayish-yellow viscera and multiple areas of submucosal and subserosal hemorrhage throughout the body (2). The autopsy findings in this case are intriguing. What was the cause of the intense blue pigmentation of the vasculature, viscera and neck? Was this some soluble antidote he was given that stained organs and vasculature (and spilled onto neck)?

The Use of Ice per Rectum in Narcotic Poisoning

The March 1901 issue of Merck's described a rather different approach to opioid intoxication. Dr.

Willis Cummings gives an anecdotal report of his experiences on the use of ice per rectum for the treatment of narcotic poisoning, a remedy he claimed success with over 18 years.

In one case, he describes a merchant who ingested 2 oz of laudanum and was found 3 hours later unconscious with hypoventilation, bradycardia and miosis. "I stripped him and had an assistant reverse him by standing on the bed and holding him up by the legs. This caused him to make an inarticulate sound, but upon introduction of a piece of ice in the rectum there was an explosively uttered profane word..." Other treatment included atropine, "the usual beating with wet towels" and continual tactile stimulation. The patient received at least one more ice and inversion treatment prior to a full recovery.

By several other cases he described use of narcotic refers to sedating agents in general, and not opiates in particular. Other cases he reports success with this treatment included chloral hydrate, chloroform and coal gas (carbon monoxide, methane and other hydrocarbons).

In a subsequent issue Dr. W. H. Lyne recommends tickling the patient with opium poisoning. He claimed this is as efficient as flagellation and less cruel, resulting in no marks or bruises.

Fortunately today we have more humane ways to support and arouse our opiate-intoxicated patients beyond noxious stimuli.

1. *Merck's Archives of Materia Medica and Drug Therapy, Vol. 3, 1901, Merck & Co., New York, University Place.*

2. *Gonzales TA, Vance M., Martland HS. Legal Medicine and Toxicology (1937), D. Appleton-Century Co., New York.*

3. *Sullivan Jr., JB, Krieger GR, editors (2001). Clinical Environmental Health and Toxic Exposures. 2nd ed. Philadelphia: Lippincott Williams & Wilkins. Chapt. 115.*

4. *Transactions of the American Pediatric Society, Vol. XII, 1900, A. G. Sherwood & Co. New York.*

5. *Nostrums and Quackery, 2nd ed. (1912) American Medical Association Press, Chicago.*

6. *Flomenbaum N.E., Goldfrank L.R., et. al., editors (2006). Goldfrank's Toxicologic Emergencies. 8th ed. New York: McGraw-Hill Chant 107*

Upcoming Meetings

NACCT 2009
September 21-26
San Antonio, Texas
www.clintox.org

American Occupational Health Conference
ACOEM Annual Scientific Meeting
April 26-29, 2009
San Diego, Ca
www.acoem.org/conferences.aspx

XXIX International Congress of the European
Association of Poisons Centres and Clinical
Toxicologists
May 12-15, 2009
Stockholm, Sweden
www.eapcct.org/show.php?page=congress

Venom Week 2009
June 1 - 4, 2009
Albuquerque, NM
<http://hsc.unm.edu/conf/venomweek2009/>

Society of Forensic Toxicology
SOFT 2009
October 18 - 23, 2009
Oklahoma City, OK
<http://www.soft-tox.org/>

Societe Francaise pour l'Etude des Toxines
17th Meeting on Toxinology
"Toxins and Signalling"
Pasteur Institute, Paris, France
December 2-3, 2009
<http://www.sfet.asso.fr/>