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TOXICOLOGY TODAY

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MANAGEMENT OF WARFARIN OVERDOSE AND SUPRATHERAPEUTIC INR

by Megan Tolman, PharmD Candidate

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Patient Case

A 21-year-old woman presented to the emergency department after a multiple drug overdose. Her INR upon arrival was 6.3 and she exhibited no signs or symptoms of bleeding. She takes warfarin therapeutically for a bilateral pulmonary embolism that occurred eight months prior. The warfarin was held for 24 hours, no vitamin K was administered, and a repeat INR was 4.8. The patient was then discharged to an inpatient psychiatric unit.

Introduction

Warfarin, an oral anticoagulant, has a narrow therapeutic range and highly variable patient response; therapeutic doses of warfarin can vary by 200-fold or more. As a result, the dose required for warfarin toxicity is also highly variable. Factors contributing to this variability include health status, food intake, alcohol use, genetic disposition, and concomitant medications.[1, 5]

The Institute for Safe Medication Practices reported 161 warfarin-associated hemorrhagic events in the first quarter of 2008.[2] The annual incidence of major bleeding events associated with warfarin therapy is estimated to be 1-10%[4]. The American Association of Poison Control Centers reported the following warfarin exposure data in 2007:[3]

- Warfarin-only cases: 2,353
- Cases in adults :1,073
- Intentional: 163
- Deaths: 3 (all unintentional)

These events were associated with normal therapeutic use, intentional exposures, and unintentional warfarin poisoning.

Full reversal of warfarin-induced coagulopathy is indicated in patients who do not require warfarin therapy. However, special consideration must be given to patients who require therapeutic anticoagulation in the event of a warfarin overdose. The purpose of this discussion is to review treatment guidelines for these patents.

Warfarin Poisoning

Warfarin inhibits the activation of blood coagulation factors; it will not affect already active clotting factors. Therefore, no coagulapathy will be noted immediately following acute warfarin ingestion. Peak anticoagulation occurs when active clotting factors are cleared from the blood and may take 2-3 days to be reflected by the INR. Anticoagulation may persist for 7 days after exposure.[4, 6]

The half-lives of the affected clotting factors are listed below:

- Factor VII: 6 hours
- Factor IX: 24 hours
- Factor X: 36 hours
- Factor II: 50 hours

The INR serves as a marker of clotting ability. A change from baseline INR should occur by 48 hours after warfarin ingestion and

(cont. on pg. 3)

IN THIS ISSUE

DID YOU KNOW?

The **Utah Poison Control Center's** emergency telephone number (800-222-1222) main menu was recently revised to facilitate quicker response by a specialist in poison information. The old multi-tier menu was consolidated into the following four menu options:

1. Emergency (all calls for consultation regarding a possible poison exposure)
2. Tablet identifications
3. Public education material and presentation requests
4. All other calls

Of important note, there is no longer a separate menu option for health care professionals. Health care professional should choose the "1 – Emergency" option to speak with a specialist in poison information regarding a patient or for a question. The redesigned menu assumes the caller is English speaking, unless the caller selects the Spanish option. New hold messages were also added to remind callers to have product containers in hand when calling the poison control center. It is our hope that the streamlined menu will be more efficient for all our callers, including health care professionals.

OUTREACH EDUCATION

HOLIDAY HAZARDS

As the holiday season approaches, the Utah Poison Control Center wants to remind you about some of the hazards during the holidays. The holidays are full of celebrations, decorations, visitors, and food, all of which may create potential hazards to children and adults. Please take the opportunity to share this information about potential hazards with your patients. We believe that awareness is the key to prevention! Access a handout that can easily be shared at: http://uuhsc.utah.edu/poison/media/HolidayHazards.pdf .

FOOD SAFETY

Foodborne illness often shows up as flu-like symptoms such as nausea, vomiting, diarrhea, or fever. Age and physical condition place some persons at higher risk than others for any type of bacteria. Symptoms usually occur between 1 hour and 3 weeks after eating contaminated food.

There are four basic food safety steps to help reduce the risk of foodborne illness:

- **CLEAN** – wash hands and surfaces often
- **SEPARATE** – don't cross contaminate
- **COOK** – cook to proper temperatures
- **CHILL** – refrigerate promptly

For more on food safety, check the following website: www.foodsafety.gov/

TOXIC DECORATIONS

Source: Steve Baskauf, USDA Forest Service

- Mistletoe and holly berries may be poisonous if swallowed.
- Lamp oils are colorful and attractive to children. If swallowed, these oils can be easily aspirated.
- Tinsel/icicles are non-toxic, but may cause airway or bowel obstruction. Old tinsel may contain lead.
- Glass ornaments are easily broken and may cause lacerations if swallowed.

- Fireplace color crystals are metallic chemicals that are irritating and may cause burns if swallowed.
- Poinsettia, thought by some to be toxic, is a very safe plant. It may cause varying degrees of irritation to the mouth and stomach if a large amount is ingested.
- Bubble lights are filled with alcohol or other solvent. Beware of broken glass if a child bites into a bulb. Eye and skin irritation may result from contact with the chemical. Some contain methylene chloride which may be harmful if swallowed.

MEDICATIONS

- There is no such thing as a childproof lid. Medicine bottle lids are only child-resistant. Keep all medicines locked up.
- Be aware when you are hosting visitors, or visiting other homes, of potential hazards to small children including medications that may not be in child resistant containers.
- Read labels carefully. Many cough and cold preparations have similar ingredients and also include analgesics such as ibuprofen and acetaminophen. Using more than one product may result in unintended double dosing due to the same or similar ingredients in different products.

MISCELLANEOUS

- Pay special attention to toys with button batteries. They can be easily swallowed or inhaled and cause burns.
- In the garage, items such as antifreeze, windshield washer fluid, and ice melts pose a risk to children and pets. Keep them out of reach of children.
- Remember that even a small amount of alcohol can be toxic to small children. Empty all cups and glasses after guests leave.

POISON PEARLS

COCAINE TOXICITY & TREATMENT

Erika Schroeder, MD, MPH
Emergency Medicine Resident

Cocaine is the most frequent cause of ED visits related to illicit drug use. It increases norepinephrine, serotonin and dopamine levels at the nerve terminals. Cocaine is most commonly smoked but is also injected, nasally insufflated and rarely ingested. Chest pain is the most common chief complaint.

Patients exposed to toxic amounts of cocaine present with a stimulant toxidrome: anxiety, agitation, mydriasis, hypertension, tachycardia, hyperthermia and diaphoresis. Benzodiazepines are the mainstay of treatment. Beta-blockers are contraindicated. For ventricular arrhythmias give sodium bicarbonate. Sodium nitroprusside is indicated for severe hypertension. Patients that are hyperthermic should undergo active cooling.

GI decontamination with activated charcoal is appropriate for ingestion of cocaine. In the case of body stuffers or packers, whole bowel irrigation is indicated to facilitate removal. If the packets are leaking, surgical removal may be necessary. Drug packing can also lead to a number of GI complications including bowel obstruction and perforation. When in doubt, manage these patients aggressively and involve surgery early in their care.

INHALANT ABUSE

Luisa Todd, MD
Emergency Medicine Resident

Inhalant abuse is a widespread problem, particularly in adolescent males of lower socioeconomic status. Volatile substances are present in numerous over-the-counter products. Clinical manifestations, which can be fatal, include CNS depression, pneumonitis, and cardiac arrhythmias due to sensitization of the myocardium to catecholamines. Toluene abuse can result in cardiac arrhythmias, renal tubular acidosis, electrolyte abnormalities, and chronic neurologic sequelae with long-term abuse. Trichloroethylene abuse can result in cardiac arrhythmias and hepatotoxicity. Nitrite inhalation can cause methemoglobinemia that may warrant methylene blue therapy. Physicians should pay careful attention to the potential for severe pulmonary complications as well as cardiovascular effects. Vasopressors should be avoided if possible due to the danger of potentiating cardiac arrhythmias.

(cont. from pg. 1)
significant exposures can be ruled out at that time if no INR change occurs.[6]

Treatment Options for Supratherapeutic INR

Supratherapeutic INR values can be reversed in several ways: omit warfarin doses, administer vitamin K, or supplement deficient clotting factors.

Vitamin K acts as a competitive inhibitor of warfarin and a substrate of vitamin K reductase, an enzyme responsible for activation of several coagulation factors.[5, 6] Complete reversal of supratherapeutic INR values can be achieved within 24-48 hours following the administration of oral vitamin K (phytonadione) and within 12-24 hours with intravenous vitamin K. Intravenous administration is reserved for patients with serious active bleeding. (Figure 1)

Fresh frozen plasma supplements all clotting factors. Administration requires ABO blood-type matching and intravenous fluids. Recombinant factor VIIa supplements only factor VII and is not FDA approved for this indication. Finally, prothrombin complex concentrates supplement the factors inhibited by warfarin (II, VII, IX, and X). This treatment option is currently undergoing clinical trials and promising results have been seen.[8, 9]

Warfarin Toxicity with Signs or Symptoms of Bleeding (Figure 1)

Treatment decisions for these patients are strongly based on risk versus benefit. If the risks associated with acute bleeding outweigh the possible risk of thrombosis, then reversal of anticoagulation is indicated.

Vitamin K should be administered via slow IV push (maximum rate 1 mg/minute) to avoid anaphylactic reactions[7] in patients with significant bleeding and preferably in a critical care setting. The INR reversal may take 6-24 hours.[8, 9] The utilization of other reversal agents will depend on the presence of life/limb-threatening bleeding events and the clinical urgency of the situation.

Warfarin Toxicity without Signs or Symptoms of Bleeding (Figure 2)

Patients with INR values slightly above the target range can expect to resume therapeutic values within 24 hours if warfarin is held during that time period.[10] However, if the INR is only slightly elevated (by < 1) holding the dose may result in subtherapeutic INR, a potential risk of thrombosis, and necessitate short-term heparin therapy.[11] Patients who have the fastest INR recovery times are typically young and have weekly doses greater than 50 mg/week.[12] Additionally, withholding warfarin doses when INR values are greater than 9.0 is usually insufficient to resolve supratherapeutic INR values and mitigate hemorrhage risk; therefore, vitamin K should be administered concurrently.

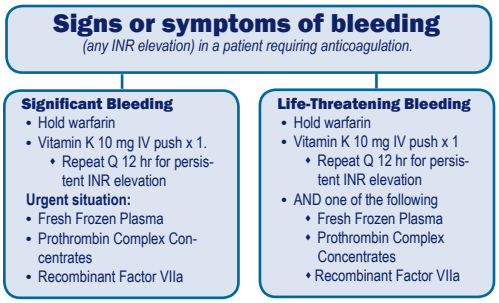
Risk factors for failure of INR resolution include: higher age (increased by 18% for each decade of life), higher baseline INR (increased 25% for each unit increase above 2.5), decompensated heart failure, active cancer, use of medications that potentiate warfarin, and limited oral intake.[12]

Those at highest risk are greater than 80 years old and require 15 mg or less of warfarin per week. Some of these patients have been identified as having vitamin K reductase gene variants that have a high affinity for warfarin.[5, 6] Early, low-dose vitamin K plays a significant role in the treatment of these patients.[12] Future study of the pharmacogenomic handling of warfarin overdose will be interesting to follow.

Conclusions

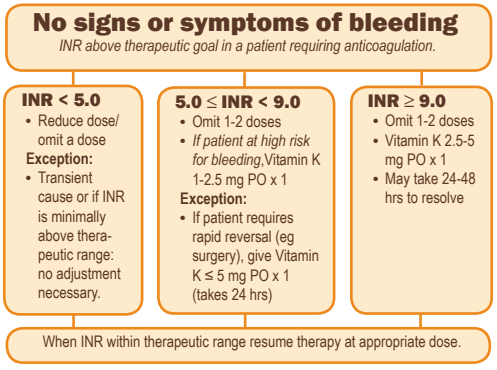
Patients with highly elevated INR values while using warfarin therapeutically require careful utilization of antidotal therapies to prevent bleeding episodes while avoiding thrombotic risk. Guidelines from American College of Chest Physicians provide evidence-based, straight-forward recommendations for treating such patients. In addition, there may be a role for pharmacogenomics in the future treatment of supratherapeutic warfarin.

Figure 1



Adapted From: Ansell J, Hirsh J, Hylek E, et al. Pharamcology and Management of the Vitamin K Antagonists. Chest 2008;133:160S-198S. Recommendations: 2.4.1, 2.4.2, 2.4.3 and 2.4.5

Figure 2



Adapted From: Ansell J, Hirsh J, Hylek E, et al. Pharamcology and Management of the Vitamin K Antagonists. Chest 2008;133:160S-198S. Recommendations: 2.4.4 and 2.4.5

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TOXINS IN THE NEWS

MEDICAL PATCHES:

The FDA has warned that **medicated patches** with metallic backings can cause **skin burns during MRI exams**. These patches include both prescription and OTC products, including nicotine patches. Patches should be removed before the exam and replace it afterwards.

http://www.fda.gov/medwatch/safety/2009/safety09.htm#Transdermal

HYDROXYCUT:

FDA warned consumers to immediately stop using **Hydroxycut** products by Iovate Health Sciences, Inc. They are dietary supplements marketed for weight-loss, as fat burners, as energy-enhancers, as low carb diet aids, and for water loss under the Iovate and MuscleTech brand names.

The FDA has received at least 23 reports of serious health problems ranging from jaundice and elevated liver enzymes to **liver injury** requiring liver transplant. Other health problems reported include seizures and rhabdomyolysis. The agency has not yet determined which ingredients, dosages, or other health-related factors may be associated with risks related to these Hydroxycut products.

http://www.fda.gov/medwatch/safety/2009/safety09.htm#Hydroxycut

Checkout our website for more poison prevention information at **www.utahpoisoncontrol.org**

MEET THE UPCC STAFF

KELLY TEEMANT, BS

graduated in May 2008 from the University of Utah in Health Promotion and Education. Since graduating, she has been working as the Project Coordinator for The Utah Poison Control Center. Kelly recently took the Certified Health Education Specialist (CHES) exam in October and is waiting patiently to see if she passed. On her days off she also works for Primary Children's Medical Center, in the PICU, as a Critical Care Tech. Kelly is a spunky, fun loving girl from Sandy, Utah who loves anything RED! She loves to learn and constantly tries new things. From the indoors, where she loves to cook/bake, read, watch movies and relax; To the great outdoors, where she isn't afraid to get dirty, you'll find her four wheeling, playing paintball, wakeboarding and snowboarding among other exciting adventures. Not much can intimidate Kelly; she's been skydiving and paragliding and said she would do both again in a heart beat! She also loves to travel and wants to see the world. Kelly and her husband of almost 3 years can't wait to take their next trip together, hopefully somewhere warm! On a more poisonous note, Kelly's favorite toxic critter is a scorpion. Kelly loves life and is very happy to be a part of the Utah Poison Control Center.

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*CSPI denotes Certified Specialist in Poison Information.

THANK YOU

The Utah Poison Control Center expresses its sincere thanks to the health care professionals, public health officials and toxicology colleagues that work together to treat and prevent poisonings.

UNIVERSITY OF UTAH COLLEGE OF PHARMACY

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