The Art of Warfarin: Oral anti-coagulant
Poster team: Tamara Brandl, Angela Colella, Carissa Drewa  Jmol team: Jeremy Bartelt , Travis Kranes, Benjamin Mattila  Educators: Daniel S. Sem, PhD, Ernest S. Stremerski, MD, MBA
Concordia University Wisconsin School of Pharmacy, Mequon, WI
Preceptors: Amy Van Abeel, PharmD, Ann Patton PharmD, BCPS, Matthew Paul RPh, Amanda Staeber PharmD, Anne Hammell PharmD, Mark Trinkl RPh, John Diedrich PharmD, and E. Merle Johnson, Pharm D, PhD

Case Synopsis
The interaction between warfarin and phenytoin can produce interesting and unpredictable results:
- A 74 year old man on long-term warfarin therapy (6mg/d) was admitted to the hospital for toxic/cloacal seclusions and started on phenytoin 300 mg/d
- INR (measure of blood coagulation) was within therapeutic range at admission
- One week after admission, providers identified an abdominal mass (patient’s INR was supratherapeutic at 10.4) and his phenytoin was 10mg/L (within normal range)
- Three days later the patient died, likely due to high INR levels from the interaction of warfarin and phenytoin (no drug levels were provided at time of death)  

While superficially, it may be easy to explain this man’s death, warfarin and phenytoin do not interact the same in every patient. Evaluating the mechanisms and sources of drug interactions may help practitioners reduce morbidity and mortality in patients on warfarin.

Molecular Story
Function of Warfarin:
- anticoagulant that inhibits vitamin K epoxide reductase (VKOR)
  - used in prophylaxis prevention of venous thromboembolism, stroke, and pulmonary embolism
  - reduce morbidity and mortality following myocardial infarction
- Why model warfarin?  
  - many drug interactions can be understood through the structure of many drugs compete at the same HAS binding site
- genetic polymorphisms of VKORC1 can result in need for an altered dosing regimen
- Why was our mentor interested in warfarin?  
  - For these reasons that patients on warfarin therapy must be closely monitored for potential drug-drug interactions.

What do we know about this molecule?

Possible Warfarin-Phenytoin Interactions

Interaction | Consequences | Adjustments
--- | --- | ---
Phenyl displaces warfarin from albumin binding sites | Increased bleeding risk from decreased warfarin levels | Decrease warfarin dosing
Phenyl increases warfarin metabolism | Increased risk of clotting from decreased warfarin levels | Increase warfarin dosing

History of Warfarin
- University of Wisconsin researchers Karl Paul Link, PhD and Harold Campbell isolated the crystallographic structure of sweet clover’s coumarin component.
- Link and Campbell published the first information about the “hemorrhagic agent” including its structure and how to extract it.
- Link and Burnberry published the chemical composition of coumarin: 3,3’-methylenebis-4-hydroxycoumarin.
- Link studies more than 100 variations of coumarin backbone, finding 3-phenylacetyl ethyl, 4-hydroxycoumarin – warfarin.
- Dimcarol, the first human anticoagulant, is FDA approved for use.
- Warfarin is FDA approved as an oral anticoagulant.
- Warfarin mechanism of action is published.
- Warfarin -R- and -S- conformational binding to albumin is published.

Unaddressed Clinical Issues
- Coumadin was synthesized by altering the structure of the natural anticoagulant drug, dicoumarol (Figure 5)
- Explore syntheses focused on making the drug structure more like Vitamin K, since it is what the body likes
- Replacing the benzyl moiety with a short, unsaturated aliphatic chain would make the drug more lipophilic, and similar to the side chain found on the Vitamin K molecule (Figure 6)
- This could lead to a drug more potent than warfarin

Albumin, Warfarin, and Phenytoin

Human serum albumin (HAS)  
- A transport protein found throughout the body  
- Critical for the distribution and transportation of many drugs
- Contains 3 domains (I, II, III) comprised of alpha helices, each of which are further divided into 2 subdomains A and B
- Has a limited number of binding sites which can result in competition between drugs for the sites
  - Warfarin  
    - A highly protein-bound drug (99%)  
    - Binds to the Sudlow site 1 (warfarin – azapropazone binding site) on the HSA IIA domain
    - Binds to HSA primarily through hydrophobic interactions, along with a few specific electrostatic interactions
  - Phenytoin  
    - Also a highly protein-bound drug
    - Binds to the Sudlow site 1 on HSA, resulting in direct competition with warfarin for the binding site

Consequences of Binding Competition

The effects of warfarin are both increased and decreased in the presence of phenytoin:
- At first there is more unfractioned warfarin present in the blood and therefore the anticoagulant effect is increased.
- This can lead to life threatening bleeding.
- If the patient does not have a bleeding episode, they may later be at risk for clotting.
- Phenytoin induces the CYP450 enzyme CYP2C9 which metabolizes warfarin.
- This increased enzyme activity metabolizes warfarin at a much faster rate, decreasing the anticoagulant effect.
- It is for these reasons that patients on warfarin therapy must be closely monitored for potential drug-drug interactions.

Adverse Effects

Adverse effects of the warfarin / phenytoin interaction include an increased risk of bleeding, as well as clot formation, uncontrolled atrial fibrillation, and an increased risk of stroke, pulmonary embolism, and myocardial infection.

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Bibliography

Figure 1: Vitamin K cycle
Figure 2: HSA with warfarin binding site
Figure 3: Warfarin bound to HSA
Figure 4: Basic structure of warfarin
Figure 5: Dicoumarol
Figure 6: Vitamin K