Cases in Drug Interactions with Anticoagulation Therapy

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Faculty Disclosure

Dr. Hritcko has no actual or potential conflicts of interest associated with this presentation

Learning Objectives

- Identify clinically significant drug interactions with anticoagulation therapy
- Discuss drug interactions that patients may hear about, but are generally not clinically significant
- Analyze cases to determine if a drug interaction is clinically significant
- Formulate plans for the identified drug interactions in simulated cases
- Formulate monitoring parameters for the identified drug interactions in the simulated cases

Magnitude of Warfarin Interactions

- Warfarin prescribing information identifies >230 reported drug interactions
  - Many more should be anticipated
  - >300 known/reported DIs mentioned in one major medical reference (Micromedex Healthcare Series)
- Until proven otherwise, all new drug entities should be carefully monitored
- Interactions can be severe (potentially life-threatening)
  - Narrow therapeutic index of warfarin
- When used properly, warfarin has been shown to be safe and effective anticoagulation therapy

Auditon Question

You are not familiar with drug X. How would you determine if a drug interaction is likely between drug X and warfarin?
- a. Check drug X prescribing information
- b. Evaluate metabolic characteristics of drug X
- c. Review case reports through medline
- d. Request information from the manufacturer’s of warfarin
- e. All of the above

Coumadin (warfarin)

- Synthesized at University of Wisconsin
- Derived from Wisconsin Alumni Research Foundation and ARIN from “heparin”
- Reversibly binds and inhibits enzymes which convert inactive vitamin K to active vitamin K
- Decreases production of vitamin K-dependent clotting factors II, VII, IX, and X
- Decreases production of natural anticoagulants protein C and S
**Vitamin K Mechanism of Action**

- **Vitamin K cycle**: Warfarin blocks the conversion of vitamin K epoxide to vitamin K.

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**Warfarin Pharmacokinetics**

- **Racemic mixture of R- and S-warfarin**
- **S-warfarin 5x more potent, but eliminated more rapidly**
- **Well absorbed (100% bioavailability)**
- **Highly protein bound to albumin**
- **Metabolized by:**
  - S-warfarin-2C9
  - R-warfarin-1A2, 2C19, 3A4
- **Average half-life 36-42 hours**

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**Warfarin Metabolism**

- **CYP-1A2**: primary
- **CYP-3A4**: minor
- **CYP-2C9**: very minor
- **CYP-2C19**: very minor

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**Mechanisms for Drug Interactions**

- **Pharmacokinetic Mechanisms**
  - **Enzyme inductions or inhibition**
    - Induction: metabolic activity is enhanced
    - Inhibition: metabolic activity is diminished
  - **Protein binding**
    - Protein bound drugs are inactive
    - If a second drug displaces warfarin from it’s binding sites, anticoagulation may be enhanced

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**Pharmacokinetic mechanisms of drug interactions**

- **Reduced absorption/bioavailability**: cholestyramine
- **Alterations in protein binding**: phenytoin
- **Alterations in metabolism**
  - Enzyme induction: rifampin, barbiturates, carbamazepine
  - Enzyme inhibition: fluconazole, cimetidine, erythromycin, ciprofloxacin
Pharmacokinetic mechanisms of drug interactions (cont.)
- Stereoselective alterations in metabolism (R or S enantiomer)
  - S is 5 times more potent
  - metronidazole (S), SMP-TMP (S), omeprazole (R), cimetidine (R),
  - amiodarone (R & S)
- Alterations in plasma clearance or excretion
  - Thyroid hormones (ex. levothyroxine)

Pharmacodynamic mechanisms of drug interactions
- **Drug synergism**: increased risk of bleeding
  - Antiplatelet drugs (ex. clopidogrel)
  - NSAIDS including COX-2 Inhibitors
- **Drug antagonism**: block absorption of warfarin, supplementation of vitamin K
  - Enteral feeds
  - Dietary supplements

Enzyme Inhibitors P450

<table>
<thead>
<tr>
<th>CYP1A2</th>
<th>CYP3A4</th>
<th>CYP2C9</th>
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<tbody>
<tr>
<td>Cimetidine</td>
<td>Clarithromycin</td>
<td>Amiodarone</td>
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<tr>
<td>Ciprofloxacin</td>
<td>Fluconazole</td>
<td>Metronidazole</td>
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<td>Erythromycin</td>
<td>Erythromycin</td>
<td>SMZ-TMP DS</td>
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<td>Zileuton</td>
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Enzyme Inducers P450

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<tr>
<th>CYP1A2</th>
<th>CYP3A4</th>
<th>CYP2C9</th>
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<tr>
<td>Cigarette smoke</td>
<td>Griseofulvin</td>
<td>Phenytoin</td>
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<td>Primidone</td>
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<td>Rifampin</td>
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Drug interactions with OTC’s
- **Examples:**
  - NSAIDS (IBU, Naproxen, ASA)
  - APAP
  - Omeprazole
  - Cimetidine
  - Bismuth subsalicylate (Salicylates)
  - Dietary Supplements (Ensure, Boost)

Warfarin interactions with OTCs
- **NSAIDs** (ex. IBU, ASA, Naproxen)
- **Caution when NSAIDs administered with warfarin**
  - NSAIDs inhibit platelet aggregation
    - ASA – Irreversible inhibition (life of the platelet)
    - Other NSAIDS (ASA, Naproxen) – Reversible inhibition
  - NSAIDs can cause GI ulcers
    - Resulting in bleeding
    - Specific drug-drug interactions may alter PT/INR
**Warfarin-APAP interactions**
- Suggested in case reports
- Verified in clinical trials
- Mechanism: Unknown – possible enzyme inhibition with increased INR
- Comparative to Warfarin-ASA/NSAIDs
  - Inhibit platelet function
  - Injury to GI mucosa

**Factors Affecting Sensitivity to Warfarin**

*Increase INR*
- Hyperthyroidism
- Low Vitamin K diet
- Malnutrition
- Age > 75yo
- Diarrhea/vomiting
- Acute Infection
- Acute ETOH use
- Stress

*Decrease INR*
- Hypothyroidism
- High Vitamin K diet
- Tobacco (cigarettes)
- Chronic ETOH use

**Drug Interactions with Dietary Supplements**
- Herbal/Botanical Products
  - Herbal products may affect the coagulation system
  - May enhance or diminish warfarin activity
    - Anticoagulation
    - Platelet actions
  - Few studies have evaluated warfarin-herbal interactions
  - Manufacturing of herbals is not scrutinized by the FDA

**Drug Interactions: Patient Considerations**
- Consider how the drug works, metabolism, and protein binding
- Intensified monitoring
  - Initiation of concomitant drug therapy
  - Discontinuation of concomitant drug therapy
- Drug history
  - Prescription Meds
  - PRN Meds
  - OTC and supplements/herbals

**Drug Interactions: Patient Considerations (cont.)**
- Absence of evidence is not evidence of absence
- There is no such thing as a “typical response” to a drug interaction
- Expect variability
  - in patient susceptibility
  - in magnitude of response
  - in time of onset
  - in duration of effect

**Monitoring Pearls**
- Do not assume an interaction will not occur just because it has not been reported
- Consider metabolic characteristics of all new drugs and their potential to interact with warfarin
- Evaluate drug therapy at every visit regardless of INR
New Oral Antithrombotic Drugs

**DRUG INTERACTIONS**

### Anti-factor Xa inhibitors
- Rivaroxaban (Xarelto)
- Apixaban (Eliquis)

### Direct thrombin inhibitors
- Dabigatran (Pradaxa)

#### Dabigatran (Pradaxa)
- The concomitant use of Pradaxa with P-gp inducers (e.g., Rifampin) reduces exposure to dabigatran and should generally be avoided. The concomitant use of P-gp inhibitors such as ketoconazole, verapamil, amiodarone, quinidine, and clarithromycin do not require dose adjustments.
- Not metabolized by CYP-450 isoenzymes

#### Rivaroxaban (Xarelto)
- Rivaroxaban is a substrate of P-glycoprotein (P-gp) and is metabolized primarily by CYP3A4. Inhibitors and inducers of these CYP450 enzymes or transporters may lead to changes in rivaroxaban exposure.

#### Drugs that inhibit CYP3A4 enzymes and drug transport systems: Avoid concomitant administration of Xarelto with combined P-gp and strong CYP3A4 inhibitors (e.g., Ketoconazole, Itraconazole, Lopinavir/Ritonavir, Ritonavir, Indinavir/Ritonavir, and Conivaptan), which cause significant increases in rivaroxaban exposure that may increase bleeding risk.
Apixaban (Eliquis)

- Apixaban is a substrate of both CYP3A4 and P-gp.
  - Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding.
  - Inducers of CYP 3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke or VTE exacerbation

Case Presentation #1

- AT is an 86yo female being followed by the anticoagulation clinic for the indication of A.Fib.
- PMH: A.Fib, HN, Hypercholesterolemia, DM-II, gout
- Current Rx Meds:
  - Allopurinol 300mg 1 tab once daily
  - Furosemide 40mg 1 tab once daily
  - Metoprolol Succ 150mg 1 tab twice daily
  - Potassium Cl 20mEq once daily
  - Hydralazine 25mg 1 tab q 8h
  - Novolin 70/30 insulin 55U AM & 40U PM daily
  - Rosuvastatin 5mg 1 tab every other day
  - Clopidogrel 75mg 1 tab once daily

Case Presentation #1 (cont.)

- OTC Meds
  - APAP PRN
  - MVT
  - Green Tea
- Anticoagulation
  - Warfarin 5mg one tab daily x 1 yr
- The Anticoagulation Clinic is informed that the following med is being added to AT’s med list:
  - Amiodarone 400mg bid

Audience Questions Case #1

- How many potential drug interactions can you identify in AT’s med list?
  - a. One
  - b. Two
  - c. Three
  - d. Four or more

Audience Questions Case #1

- When should we schedule AT’s next PT/INR visit?
  - a. Recheck INR in 1 month
  - b. Recheck INR in 2 weeks
  - c. Recheck INR in 5 days
  - d. Recheck INR tomorrow
Case Presentation #2

- ML is a 67 yo male with recent idiopathic DVT
- PMH: HTN, DM-II, Hypercholesterolemia, elevated triglycerides
- Anticoagulation:
  - Warfarin 10mg Tu, 5mg W, Sa, 7.5mg X 4d
- OTC Meds:
  - Omega-3 Fatty 1 tab daily
  - MVT with Calcium 1 tab daily
  - APAP PRN

Case Presentation #2 (cont.)

- Current Rx Meds:
  - Metformin 500mg 1 tab bid
  - Metoprolol 50mg 1 tab bid
  - Atorvastatin 80mg 1 tab daily
  - Lisinopril 40mg 1 tab bid
  - Fenofibrate 145mg 1 tab daily
  - Clonidine 0.1mg 1 tab bid
  - Amlodipine 10mg 1 tab daily
  - Isosorbide Mon 60mg 1 tab daily
  - Griseofulvin 500mg 1 tab daily x 6 weeks

Case Presentation #2 (cont.)

- The Anticoagulation Clinic is informed on that his griseofulvin med is being d/c’d effective immediately.

Audience Questions Case #2

- How many potential drug interactions can you identify in ML’s med list?
  - a. One
  - b. Two
  - c. Three
  - d. Four or more

Audience Questions Case #2

- When should we schedule ML’s next PT/INR visit?
  - a. Recheck INR in 1 month
  - b. Recheck INR in 2 weeks
  - c. Recheck INR in 5 days
  - d. Recheck INR tomorrow

Case Presentation #3

- JM is a 57 yo female with AVR
- PMH: HTN, Hypercholesterolemia, osteoarthritis
- Anticoagulation:
  - Warfarin 7.5mg MF & 5mg x 5 days
- OTC Meds:
  - MVT tab daily
  - Calcium 600mg 1 tab bid
  - APAP 1gm tid
Case Presentation #3 (cont.)

- Current Rx Meds:
  - Metropolol 50mg 1 tab bid
  - Lisinopril 40mg 1 tab bid
  - HCTZ 25mg 1 tab daily
  - Simvastatin 20mg 1 tab daily

Audience Questions Case #3

- JM decides to self-treat what is believed to be a vaginal yeast infection with miconazole nitrate vaginal cream x 7 days.

- Should you be concerned about a vaginally administered medication like miconazole with warfarin?
  - a. Yes
  - b. No
  - c. Undecided

Audience Questions Case #3

- When should we schedule JM’s next PT/INR visit?
  - a. Recheck INR in 1 month
  - b. Recheck INR in 2 weeks
  - c. Recheck INR in 3-4 days
  - d. Recheck INR tomorrow

Questions?

References

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