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

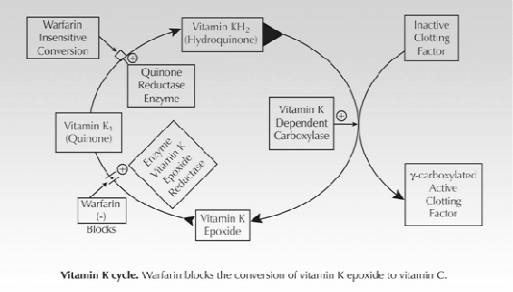
Audience Question

- 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 **W**isconsin **A**lumni **R**esearch **F**oundation 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 C.

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

WARFARIN OXIDATIVE METABOLISM

R-Warfarin	CYP-1A2	primary
	CYP-3A4	*minor*
	CYP-2C19	*very minor*
S-Warfarin	CYP-2C9	primary
	CYP-3A4	*minor*

Mechanisms for Drug Interactions

- **Pharmacokinetic Mechanisms**
  - Altered warfarin plasma concentrations
  - **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

Mechanisms for Drug Interactions

- **Pharmacodynamic Mechanisms**
- Do not alter warfarin plasma concentration
- **Synergism**: Two drugs when used in combination produce a greater effect than the individual effect of each agent when used alone
- **Antagonism**: The effect of one drug is inhibited or reversed by the activity of another drug (ex. Vitamin K and warfarin)

Pharmaco**kinetic** mechanisms of drug interactions

- Reduced absorption/bioavailability: cholestryramine
- Alterations in protein binding: phenytoin
- Alterations in metabolism
  - Enzyme induction: rifampin, barbitruates, carbamazepine
  - Enzyme inhibition: fluconazole, cimetidine, erythromycin, ciprofloxacin

Pharmaco**kinetic** 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)

Pharmaco**dynamic** 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

CYP1A2	CYP3A4	CYP2C9
Cimetidine	Clarithromycin	Amiodarone
Ciprofloxacin	Fluconazole	Metronidazole
Erythromycin	Erythromycin	SMZ-TMP DS
Fluvoxamine	Itraconazole	Fluconazole
Zileuton	Fluoxetine	Disulfiram

Enzyme **Inducers** P450

CYP1A2	CYP3A4	CYP2C9
Barbiturates	Barbiturates	Barbiturates
Carbamazepine	Carbamazepine	Carbamazepine
Cigarette smoke	Griseofulvin	Phyenytoin
Phenytoin	Primidone	Rifampin
Primidone		
Rifampin		

Drug interactions with OTC's

- Examples:
  - NSAIDS (IBU, Naproxen, ASA)
  - APAP
  - Omeprazole
  - Cimetadine
  - 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

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

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: 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

New Oral Antithrombotic Drugs

- Anti-factor Xa inhibitors
  - Rivaroxaban (Xarelto)
  - Apixaban (Eliquis)
- Direct thrombin inhibitors
  - Dabigatran (Pradaxa)



Dabigatran (Pradaxa)

- The concomitant use of Pradaxa with P-gp inducers (eg. 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

Rivaroxaban (Xarelto)

- Drugs that inhibit CYP3A4 enzymes and drug transport systems: Avoid concomitant administration of Xarelto with combined P-gp and strong CYP3A4 inhibitors (eg. Ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan), which cause significant <u>increases</u> in rivaroxaban exposure that may increase bleeding risk.

Rivaroxaban (Xarelto)

- Drugs that induce CYP3A4 enzymes and drug transport systems: Avoid concomitant use of Xarelto with drugs that are combined P-gp and strong CYP3A4 inducers (eg. Carbamazepine, phenytoin, rifampin, St John's wort) due to <u>decreases</u> in rivaroxaban exposure that may decrease efficacy

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

Patient Cases

Case Presentation #1

- AT is a 86yo female being followed by the anticoagulation clinic for the indication of A.Fib.
- PMH: A.Fib, HtN, Hypercholesterolemia, DM-II, gout
- Current Rx Meds:
  - Allopurinol 300mg 1 tab once daily
  - Furosemide 40mg 1 tab once daily
  - Metoprolol Suc 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 grisofulvin 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:
  - HCTZ 25mg 1 tab daily
  - Lisinopril 40mg 1 tab bid
  - Metropolol 50mg 1 tab bid
  - Simvastatin 20mg 1 tab daily

Audience Questions Case #3

- JM decides to 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?

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