MANAGING DRUG INTERACTIONS WITH WARFARIN

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About the presenter

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Dr. Howard reports she has no actual or potential conflict of interest in relation to this activity.

Warfarin Drug Interactions Program Overview

- Defining the problem
- Contributing factors
- Warfarin: mechanism of action, pharmacokinetics/pharmacodynamics
- Potential mechanisms for DIX
- Time course for interactions
- Examples of key interactions
- Frequency of interactions
- Management Strategies

Benefits

- Mainstay of oral anticoagulation for >60 y
- Strong evidence base for effectiveness in:
  - Prevention/treatment of venous TE
  - Prevention of embolism with prosthetic valves
  - Stroke prevention for Atrial Fibrillation
- Major adverse effect is major/minor bleeding
- Drug interactions may increase risk

Risks

- Warfarin widely used; chronic therapy
- Commonly prescribed in elderly
- Complex patients on multiple meds
- Narrow therapeutic index
- Variable individual dose response
- Multiple interaction mechanisms
- Poor understanding of warfarin pharmacokinetics/pharmacodynamics and impact on DIX

Anticoagulant Effect of Warfarin

Inactive Coagulation Factors: II, VII, IX, and X

Active Coagulation Factors

- Vitamin K-dependent Coagulation Factors
- Vitamin K

Warfarin inhibits

Vitamin K-dependent Coagulation Factors
**Factors Affecting the Dose-Response with Warfarin**

- Pharmacokinetics of warfarin
- Patient’s hemostatic response and vitamin K concentrations
- Hepatic function
- Metabolic state
- Pharmacogenomics
- Drug-Drug/Food Interactions
- Compliance

**Pharmacokinetics of Warfarin**

- Mixture of R and S (stronger) isomers
- Rapidly absorbed; oral F = 100%
- Maximal serum conc. in 1-2 hr
- Highly bound to albumin (97%)
- Metabolized by hepatic cytochrome P-450 enzymes
  - (R: CYP 3A4, 1A2, 2C19; S: 2C9)
- Avg. Half-life 40 hours

**Pharmacodynamics**:

**Variables Affecting Time to Achieve Full Antithrombotic Effect of Warfarin**

- Time required to achieve steady state plasma levels of warfarin
  - (3-5 t1/2 which avg. 40 h)
- Time required to clear circulating plasma levels of factors II, VII, IX, X

**Vitamin-K Dependent Factors**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Half-Life</th>
</tr>
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<tbody>
<tr>
<td>Protein C</td>
<td>4 hours</td>
</tr>
<tr>
<td>VII</td>
<td>6 hours</td>
</tr>
<tr>
<td>IX</td>
<td>24 hours</td>
</tr>
<tr>
<td>X</td>
<td>40 hours</td>
</tr>
<tr>
<td>II</td>
<td>60 hours</td>
</tr>
</tbody>
</table>

PT is sensitive to levels of Protein C, VII, X, II

**Warfarin Dose Response/Time Course**

**Pharmacokinetic Mechanisms for Warfarin Drug Interactions and Probable Impact on INR**

- Mechanism | INR
- Inhibit absorption | decrease
- Protein binding displacement | increase
- Inhibit Metabolism | increase
- Induce Metabolism | decrease

Pharmacokinetic changes alter warfarin serum concentrations and generally have delayed maximal effect.
Pharmacodynamic Mechanisms for Warfarin Drug Interactions and Probable Impact on INR

- Most impair hemostasis; effect may be rapid
  - Mechanism: INR
    - Increased bleeding risk: unchanged
    - Inhibition of coagulation: unchanged or increased
    - Inhibit warfarin's anticoagulant effect: decreased

Clinical Consequences of Warfarin Drug Interactions

- Most common
  - Increased warfarin effect and increased risk of major (GI, ICH) or minor bleeding
    - Hold or decrease warfarin dose + reversal
  - Less common
    - Decreased warfarin effect and increased risk of thrombosis or stroke
      - Increase warfarin dose or bridging

Time Course for Warfarin Interactions

- Typical
  - Onset within 24-72 hours
  - New steady state in 4-7 days
  - Offset in 1-2 weeks
- Key Variables
  - Dose and duration of both drugs
  - Half-lives of both drugs
  - Half-lives of clotting factors
  - Mechanism of interaction

Prescribed Drugs that may Potentiate Warfarin's Anticoagulant Effect primarily by altering hemostasis

- Antiplatelets
  - Aspirin, Salicylates
  - Clopidogrel
  - Omega-3 supplements; fish oil
  - SSRIs (some may also inhibit P450 enz)
- Anti-inflammatories: all NSAIDs
  - Weak antiplatelets but cause GI injury, erosion
  - Anticoagulants (e.g. heparin/LMWH)
  - Thrombolytics
  - Thyroid hormones

Prescribed Drugs that may Potentiate the Anticoagulant Effect of Warfarin primarily by CYP enzyme inhibition

- Cardiovascular agents
  - Amiodarone
  - Propafenone
  - Fibrates
  - Lovastatin, simvastatin
- GI drugs
  - Omeprazole
  - Cimetidine

Warfarin Interactions with Anti-infectives

- Most potentiate warfarin's effect
- Multiple mechanisms
  - CYP 450 inhibition,
    - altering vitamin K producing GI flora,
    - protein displacement
  - Broader spectrum drugs often have most pronounced effect
- Onset is fairly rapid
- Often necessitates dosage change when added and when discontinued
### Antibiotics that may Potentiate the Anticoagulant Effect of Warfarin

- Cephalosporins
- Penicillins
- Tetracyclines
- Macrolides especially erythromycin, clarithromycin
- Quinolones especially ciprofloxacin
- Sulfonamides
- TMP-SMX
- Misc: isoniazid, metronidazole

### Antifungal Drugs that may Potentiate the Anticoagulant Effect of Warfarin

- Ketoconazole
- Miconazole
- Fluconazole
- Itraconazole
- Terbinafine (?)

### Prescribed Drugs that May Decrease the Anticoagulant Effect of Warfarin

**CYP 450 ENZYME INDUCTION**

- Anti-infectives
  - Dicloxacillin
  - Nafcillin
  - Rifampin
  - Griseofulvin
- Anticonvulsants
  - Barbiturates
  - Carbamazepine
  - Phenytoin

**Inhibition of warfarin absorption**

- Bile acid sequestrants
- Sucralfate

**Antagonism of warfarin effect**

- Phytonadione (vitamin K1)

### Purpose/Methods

- Determine the frequency and types of potential warfarin drug interactions that may increase bleeding risks in patients with AF following hospitalization
- Study cohort: 704 Kansas Medicare beneficiaries discharged from acute care hospitals between 4/1/98 and 9/30/98
- Principal or secondary dx of AF
- Patient discharged on warfarin

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*Pharmacoepidemiology and Drug Safety 2002;11:569-76.*
AF patients discharged on warfarin

Nature of Interacting Drugs that Prolong INR values, N=150 Rx

Case Report: Warfarin Interaction with Trimethoprim-Sulfamethoxazole

- A 70 yr old male with history of AF/AVR taking warfarin 6 mg daily. INR had been stable with most recent value of 2.5. Patient developed sinusitis and began TMP-SMX (Bactrim DS) twice daily. After three days of TMP-SMX, he developed a large abdominal bruise.


Prevalence of Interacting Drug Prescriptions for Patients on Warfarin

Nature of Interacting Drugs that have Additive Risks for Bleeding, N=56 Rx

Warfarin/TMP-SMX Interaction (Cont)

<table>
<thead>
<tr>
<th>Day</th>
<th>INR</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>2.5</td>
</tr>
<tr>
<td>3</td>
<td>8.7</td>
</tr>
<tr>
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<tr>
<td>8</td>
<td>3.3</td>
</tr>
<tr>
<td>9</td>
<td>2.0</td>
</tr>
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</table>

Impact of Preemptive Warfarin Dose Reduction on INR when adding Antibiotic

Overall Study Findings
- Compared to controls preemptive DR prevented statistically significant increases in mean INR after addition of either levofloxacin or TMP-SMX but effect more pronounced with TMP-SMX
- Mean warfarin dose reduction was 16%

Impact of Preemptive Warfarin Dose Reduction on INR when adding Antibiotic

For controls only: 3 vit k, 1 FFP

Impact of Preemptive Warfarin Dose Reduction on INR when adding Antibiotic

Individual Patient Findings
- After DR in TMP-SMX patients:
  - 25% developed INRs > 4.0
  - 0% had subtherapeutic INR
  - Suggests need for even greater reduction in warfarin dose
- After DR in levofloxacin patients:
  - 0% developed INR > 4.0 but
  - 40% had subtherapeutic INRs
  - Suggests may be better to simply monitor INR


Impact of Preemptive Warfarin Dose Reduction on INR when adding Antibiotic

Warfarin-Amiodarone Interaction
- Amiodarone has an avg t1/2 of 53 d
- Therefore interactions with warfarin have an unpredictable time course and often have a slow onset (1-2 weeks) and offset (4-8 weeks)
- The mean increase in the INR due to amiodarone is 44% (22 to 108%). Most patients require a 50% warfarin dose reduction

Starting Amiodarone in a Patient on Warfarin: Case Report 1
- 54 yr old hospitalized patient
- Warfarin for over one year. On 4 mg, the INR was stable at 2.3
- Amiodarone started for Atrial fibrillation at 200 tid x 1 wk and then 200 mg daily
- After 5 days of amio loading, patient was discharged with INR of 2.6
- Readmitted two weeks later, with a GI bleed and INR of 5.9.

Starting Warfarin in a Patient on Amiodarone: Case Report 2
- 62 yr male hospitalized for CABG surgery
- Patient had history of atrial fibrillation
- Warfarin 5 mg daily DC'd prior to surgery
- Postop started on amiodarone 400 mg bid for 10 days and then 200 mg qd for AFib
- Warfarin restarted prior to discharge
- Readmitted 18 days later with gross hematuria
**Warfarin-Amiodarone Case 2 cont.**

<table>
<thead>
<tr>
<th>Warfarin day</th>
<th>INR</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1.1</td>
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<tr>
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<tr>
<td>24</td>
<td>7.2</td>
</tr>
<tr>
<td>28</td>
<td>1.8</td>
</tr>
<tr>
<td>33</td>
<td>2.4</td>
</tr>
</tbody>
</table>

**Nonprescription Drugs that may Interact with Warfarin**

- **Potentiate**
  - Aspirin (aspirin containing)
  - NSAIDS
  - Cimetidine
  - Omeprazole
  - Acetaminophen (?)

- **Antagonize**
  - Chronic Alcohol

**Examples of Herbals that May Potentiate Warfarin**

- Alfalfa
- Chamomile
- Cinchona Bark
- Clover Oil
- Danshen
- Dong Quai
- Feverfew
- Garlic
- Ginger
- Ginko
- Ginseng (↑↓ INR)
- St. John’s wort
- Melilot
- Red Clover
- Sweet Woodruff
- Tonka Beans
- Herbal Teas

**Managing Warfarin Interactions**

- Identify all Rx/OTC drugs, nutritional products & herbals the patient is on
- If the INR changes abruptly in a previously stable patient, screen for compliance and interactions before changing the dose
- Understand the typical time course
- Remember today’s INR reflects changes approximately 4-5 days ago

**Managing Warfarin Interactions (cont)**

- If an interacting drug is indicated consider preemptive warfarin dose reduction
- When adding or stopping potentially interacting drugs, monitor the INR at least twice weekly for two weeks and adjust the dose slowly
- Educate the patient

The potential for drug interactions with warfarin should NOT be considered an absolute contraindication for therapy but rather one factor which contributes to the patient’s overall **Benefit:Risk Ratio.**
Sponsored by:

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This material was prepared by the Kansas Foundation for Medical Care, Inc. (KFMC), the Medicare Quality Improvement Organization for Kansas, under contract with the Centers for Medicare & Medicaid Services (CMS), an agency of the U.S. Department of Health and Human Services. The contents presented do not necessarily reflect CMS policy. #9SOW-KS-PS_DS-09-14.