


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/dynamics
- Potential mechanisms for DIX
- Time course for interactions
- Examples of key interactions
- Frequency of interactions
- Management Strategies




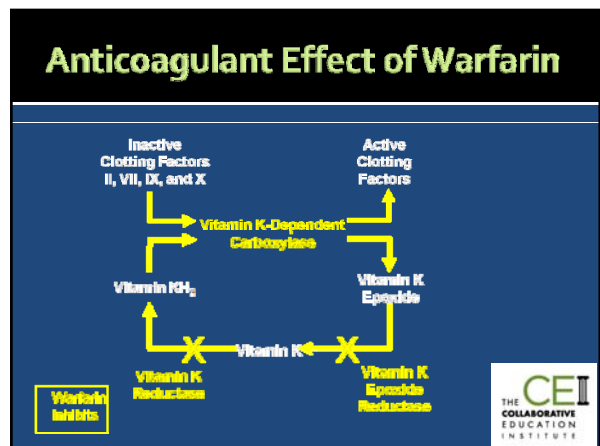
Benefits Risks

- 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



Contributing Factors to the High Risk of Warfarin Drug Interactions

- 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

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 t_{1/2} which avg. 40 h)
- Time required to clear circulating plasma levels of factors II, VII, IX, X



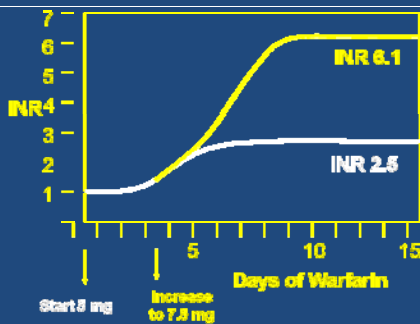
Vitamin-K Dependent Factors

Factor	Half-Life
■ Protein C	4 hours
■ VII	6 hours
■ IX	24 hours
■ X	40 hours
■ II	60 hours

■ 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

<u>Mechanism</u>	<u>INR</u>
Increased bleeding risk by alternate pathway	unchanged
Inhibition of coagulation by alternate pathway	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 | ■ Anticonvulsants |
| ▪ Dicloxacillin | ▪ Barbiturates |
| ▪ Nafcillin | ▪ Carbamazepine |
| ▪ Rifampin | ▪ Phenytoin |
| ▪ Griseofulvin | |



Prescribed Drugs that May Decrease the Anticoagulant Effect of Warfarin

Inhibition of warfarin absorption

- Bile acid sequestrants
- Sucralfate

Antagonism of warfarin effect

- Phytonadione (vitamin K1)



The Nature and Frequency of Warfarin Drug Interactions that Increase Bleeding Risk in Atrial Fibrillation Patients

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Pharmacoepidemiology and Drug Safety 2002;11:569-76.

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

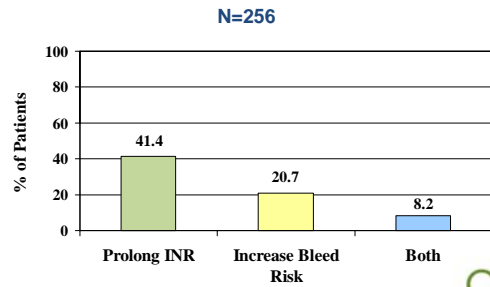


AF patients discharged on warfarin



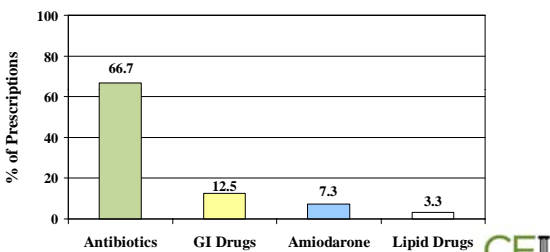
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Prevalence of Interacting Drug Prescriptions for Patients on Warfarin



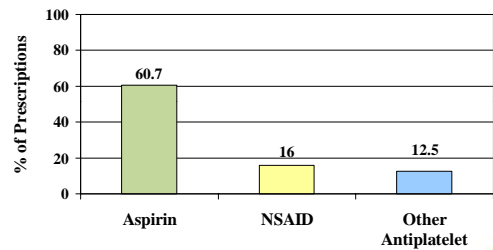
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Nature of Interacting Drugs that Prolong INR values, N=150 Rx



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



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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.

- Cook et al. J Fam Pract 1994;39:589

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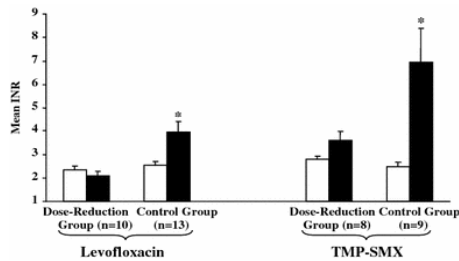
Warfarin/TMP-SMX Interaction (Cont)

Day	INR
0	2.5 TMP-SMX started
3	8.7 stop both drugs
4	9.2
5	7.0
6	4.7
7	4.7
8	3.3 restart warf. 6 mg
9	2.0

Cook et al. J Fam Pract 1994;39:589

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Impact of Preemptive Warfarin Dose Reduction on INR when adding Antibiotic



For controls only: 3 vit k, 1 FFP

Ahmed et al. J Thromb Thrombolysis 2008;26:44-48



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%

Ahmed et al. J Thromb Thrombolysis 2008;26:44-48



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

Ahmed et al. J Thromb Thrombolysis 2008;26:44-48



Warfarin-Amiodarone Interaction

- Amiodarone has an avg t_{1/2} 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 1wk 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.

Warf day	INR		
1	1.1	Warfarin 5mg; amio loading day 4	
2	1.3		
3	1.7		
4	2.2		
5	2.5		
6	2.5	Discharged, amio reduced	
24	7.2		Hematuria, warfarin held, vit K
28	1.8		
31	2.4	Discharged, repeat INR in 3 days	
33	2.4		



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.



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