MANAGING DRUG INTERACTIONS WITH WARFARIN

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About the presenter

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Dr. Howard 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

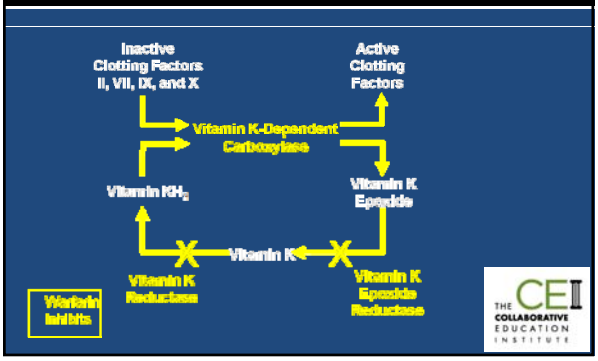
Benefits  Risks

- Mainstay of oral anticoagulation for >6o 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

Anticoagulant Effect of Warfarin



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

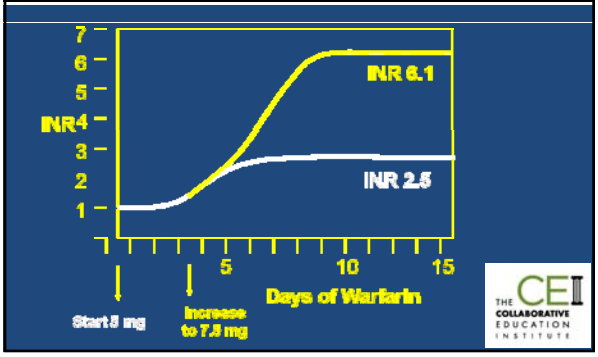
- Time required to achieve steady state plasma levels of warfarin
- (3-5 t1/2 which avg.40 h)
- Time required to clear circulating plasma levels of factors II, VII, IX,X

Vitamin-K Dependent Factors

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

Mechanism	INR
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
  - Dicloxacillin
  - Nafcillin
  - Rifampin
  - Griseofulvin
- Anticonvulsants
  - Barbiturates
  - Carbamazepine
  - Phenytoin

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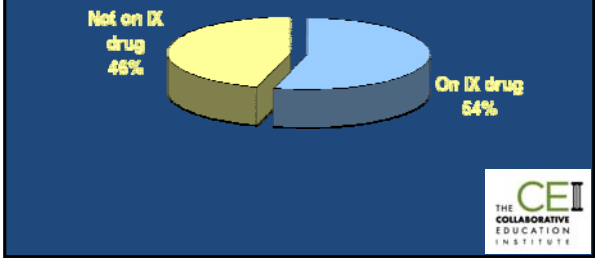
Pharmacoepidiology and Drug Safety 2002;11:569-76.

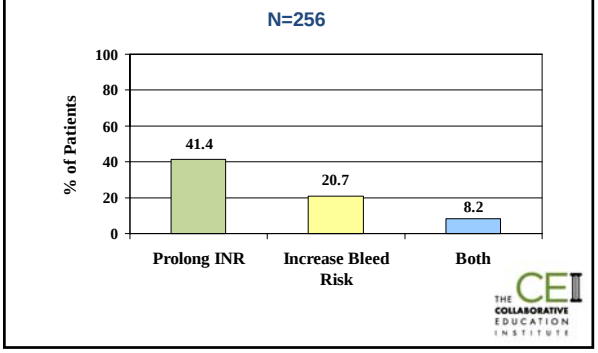
Purpose/Methods

- 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

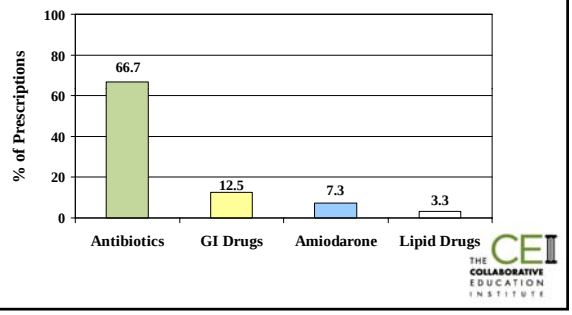
AF patients discharged on warfarin



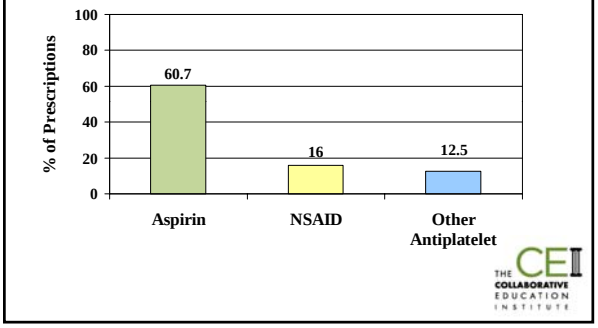
Prevalence of Interacting Drug Prescriptions for Patients on Warfarin



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



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



Case Report: Warfarin Interaction with Trimethoprim-Sulfamethoxazole

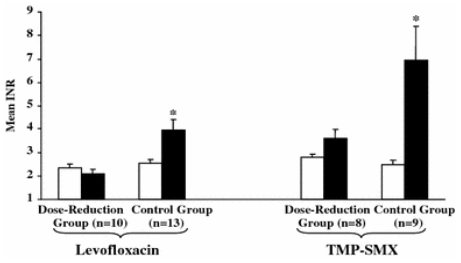
- A 70 yr old male with history of AF/AVR taking warfarin 6 mg daily. INR had been stable with most recent value of 2.5. Patient developed sinusitis and began TMP-SMX (Bactrim DS) twice daily. After three days of TMP-SMX, he developed a large abdominal bruise.
- Cook et al. J Fam Pract 1994;39:589

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

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 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 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	Restart warfarin 2 mg
31	2.4	
33	2.4	Discharged, repeat INR in 3 days

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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