Clinically Significant Cardiovascular Drug Interactions

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Introduction

• Drug interactions represent 3-5% of preventable in-hospital ADRs

• Drug interactions are a major contributor of patients seeking further medical care (ED visits and hospitalizations)

• While electronic medical records can help to minimize clinically significant drug interactions they are not fail safe
  – Alert fatigue
  – Determining the significance of interactions when alerted
Introduction

• Types of drug interactions
  – Pharmacokinetic interactions
  – Pharmacodynamic interactions
  – Pharmacogenetic interactions
  – Food-drug interactions
  – Drug-disease state interactions
Pharmacokinetic Drug Interactions

- Pharmacokinetics: How the body “handles” medications.
- Typical interactions occur that will either increase or decrease a medication when one or more are given together.
  - Absorption
  - Distribution
  - Metabolism
  - Excretion/Elimination

ADME
Cytochrome P450 Enzyme System

• Group of heme-containing enzymes

• Enzyme distribution
  – Liver
  – Gastrointestinal tract
  – Kidneys
  – Lungs
  – Brain
Cytochrome P450 Enzyme system

• Responsible for Phase I reactions
  – Oxidation reactions
    • Hydroxylation
    • Dealkylation
    • Oxidation
  – Reduction reactions
    • Azo- and Nitro-reduction
CYP Metabolism

• Drugs interact with the CYP450 system by being:
  – Substrates
  – Inhibitors
  – Inducers
Substrates

• Many medications are substrates for the CYP450 enzyme system
• Inhibition of this enzyme lead to increased levels of parent compound
• Inhibitors of a certain enzyme can also be metabolized through that same enzyme or another enzyme
Inhibitors of the CYP450

• Most commonly occurs as competitive binding
  — Competition depends on
    • Substrate affinity
    • Concentration of substrate
    • Half-life of inhibitor
  — Inhibition depends on:
    • Half-life of inhibitor
    • Time to steady state of the inhibitor
CYP2D6

• Genetic polymorphism
  – Extensive metabolizers
  – Poor metabolizers
    • 5-15 % of whites
    • 1-3 % African Americans and Asians
CYP2D6

• Inhibitors
  – Amiodarone, Propafenone, Quinidine
  – Fluoxetine, Paroxetine, Sertraline
  – Ritonivir
  – Haloperidol, Thioridazine
CYP2D6

• Substrates
  – Codeine
  – Flecainide, Mexiletine, Propafenone
  – Bisoprolol, Labetalol, Metoprolol, Pindolol, Propranolol, Timolol
CYP2C9 isoenzymes

• Genetic polymorphism
  – 20% of Asians and African Americans are poor metabolizers (PMs) whereas only 3-5% of Caucasians are PMs
CYP2C9 isoenzymes

• Inhibitors
  – Amiodarone
  – Cimetidine
  – Fluvoxamine
  – Fluconazole, ketoconazole
  – Omeprazole
CYP2C9 isoenzymes

• Substrates
  – Losartan
  – Phenytoin
  – S-warfarin (more pharmacologically active)
Inducers of the CYP450 system

- Phenytoin (3A4, 2D6, 2C9)
- Phenobarbital (3A4, 2D6, 2C9)
- Carbamazepine (3A4, 2D6, 2C9)
- Rifampin (3A4, 2D6, 2C9)
- Ritonavir (2D6)
- Smoking (1A2)
Drug Transport

• P-glycoprotein
  – Energy-dependent trans-membrane efflux pump
    • Intestines
    • Hepatocytes
    • Kidney proximal tubule
    • Blood-brain barrier
  – A number of drugs are substrates (cancer agents, digoxin, many of the newer oral anticoagulants, cyclosporine, protease inhibitors)
  – Encoded by the multidrug resistance gene (MDR-1) also called ABCB1 gene
P-glycoprotein

• Inhibitors
  – In the intestines can increase the bioavailability of certain medications
  – In the intestines and liver may lead to decreased elimination of medications

• Inducers

• Many of the medications that alter P-glycoprotein functions also can alter CYP enzyme function
P-glycoprotein

• Inhibitors
  – Clarithromycin
  – Cyclosporine
  – Erythromycin
  – HIV protease inhibitors
  – Itraconazole
  – Ketoconazole
  – Quinidine
  – Verapamil

• Inducers
  – Rifampin
  – St. John’s wort
Pharmacodynamic Drug Interactions

• Pharmacodynamics: How a drug affects the body

• Typical interactions will have either an enhanced or blunted pharmacologic effect of a medication when on or more are used together
Pharmacogenomic Drug Interactions

• Pharmacogenomic: Genetic coding of receptors, metabolizing enzymes, transporters etc.

• Alterations in a patient's genetic coded can modify the pharmacokinetics or pharmacodynamics of isolated medications.

• There are a number of identified pharmacogenomic alterations that can modify pharmacologic response
  — However, little data to help us clinically use this data.
Food Drug Interactions

• Certain medications can have alterations in pharmacology effect by addition or subtraction of certain foods

• Some foods may modify the ADME of pharmacokinetics
  – Cations and ciprofloxacin
  – Grapefruit juice and simvastatin
  – Vitamin K rich foods and warfarin
Disease State Drug Interactions

• Certain medications can be considered drug interactions with certain disease states
• These interactions can be real or anticipated
• Examples include:
  – Dronedarone and heart failure
  – Flecainide and structural heart disease
  – Cilostazol and heart failure
Individual Drug Interactions
Drug Interactions

• Amiodarone
  — Pharmacokinetic
    • Increase warfarin effects
    • Increases levels of digoxin, procainamine, quinidine, cyclosporine (CSA), phenytoin, flecainide, mexilite, propafenone, simvastatin, lovastatin, tacrolimus, etc.
  — Pharmacodynamic
    • Verapamil, diltiazem, beta-blockers, other QT-prolonging medications
Drug Interactions

Warfarin

– Pharmacokinetic
  • Drugs that increase INR
    ▪ Amiodarone, quinidine +/-, propafenone
    ▪ Trimethoprim/sulfamethoxazole, erythromycin, metronidazole, other antibiotics
    ▪ Azole antifungals
    ▪ Cimetidine

– Pharmacokinetic
  • Drugs that decrease INR
    ▪ Barbiturates
    ▪ Carbamazepine
    ▪ Rifampin
    ▪ Phenytoin
    ▪ Cholestyramine (decreased bioavailability)
Drug Interactions

• Warfarin
  – Pharmacodynamic
    • Drugs that interfere with clotting hemostasis
      • ASA and other NSAIDS
      • Antiplatelet medications
Digoxin

— Pharmacokinetic
  • Increase levels
    ▪ Amiodarone, quinidine, propafenone, verapamil, diltiazem
    ▪ Erythromycin/Clarithromycin, tetracycline
  • Decrease levels
    ▪ Antacids, Sucralfate, Cholestyramine/Colestipol

— Pharmacodynamic
  • Medications that slow heart rate (Beta blockers and calcium channel blockers)
  • Medications that cause electrolyte depletion
    • Thiazide and loop diuretics
Dofetilide

- Pharmacokinetic Interaction
  - Inhibition of cation transport
    - Cimetidine
    - Hydrochlorothiazide
    - Prochlorperazine
    - Itraconazole
    - Ketoconazole
    - Trimethoprim alone or in combination
    - Megestrol
    - Verapamil
Dofetilide

• Pharmacodynamic Interactions
  – Medications that prolong the QT interval
    – Haloperidol
    – Phenothiazine class antiemetics and antipsychotic medications
    – Certain atypical antipsychotic medications
    – Methadone
    – Many others
Newer Oral Anticoagulants

• Direct Thrombin Inhibitor
  – Dabigatran

• Factor Xa Inhibitors
  – Rivaroxaban
  – Apixaban
Dabigatran (Pradaxa)

• Renal elimination is the major route of elimination for dabigatran, however P-gp inhibition or induction may alter the systemic exposure

• Dronedarone and ketoconazole should be used cautiously with dabigatran if the patient has a creatinine clearance between 30 and 50 ml/min

• Not all P-gp inhibitors will have the same effect and may be safe (verapamil, amiodarone, quinidine)

• P-gp inducer rifampin should be avoided with dabigatran.
Rivaroxaban (Xeralto)

- Rivaroxaban is a substrate for the CYP 3A4 and P-gp and partially cleared through renal elimination
- Strong CYP 3A4 and P-glycoprotein inhibitors can increase the exposure of rivaroxaban.
  - Some combinations have been resulted in a 150 to 160% increase in drug exposure when given concomitantly.
- Strong CYP 3A4 and P-glycoprotein inducers can decrease the exposure of rivaroxaban.
Rivaroxaban (Xeralto)

• Combinations to avoid
  – Pharmacokinetic
    • Increased levels (Strong 3A4 and P-gp inhibitors)
      ▪ Ketoconazole, and fluconazole (suspect others as well)
      ▪ Ritonavir
      ▪ Clarithromycin and erythromycin
    • Decreased levels
      • Rifampin
      • Phenytoin
Rivaroxaban (Xeralto)

• Patients with renal dysfunction defined as a creatinine clearance between 15 ml/min – 80 ml/min should not receive medications that are moderate inhibitors of 3A4 and P-gp
  – Amiodarone, diltiazem, verapamil, cimetidine and erythromycin
Apixaban (Eloquis)

• Like rivaroxaban, apixaban is a substrate for CYP3A4 and P-gp and strong inhibitors will increase the levels of apixaban.

• Also, inducers will decrease the levels of apixaban

• Drugs like ketoconazole, itraconazole, ritonivir or clarithromycin will require a dosing reduction or discontinuation of therapy.
Oral P2Y12 Inhibitors

- Clopidogrel
- Prasugrel
- Ticagrelor
Clopidogrel (Plavix)

- Metabolized in a two step process to an active metabolite
Clopidogrel

- Interaction with omeprazole and other PPIs has been controversial
- There is a known pharmacokinetic interaction
- Limited data suggesting clinical relevance of interaction
- However, package insert considers combination of omeprazole or esomeprazole to be contraindicated.
Prasugrel (Effient)

• Most interactions are pharmacodynamic in nature
  – Agents that increase the risk of bleeding
    • Anticoagulants
    • NSAIDS
Ticagrelor (Brillinta)

• Pharmacokinetic
  – Strong 3A4 inhibitors
    • May increase ticagrelor levels and decrease the levels of the active metabolite
      ▪ Clarithromycin
      ▪ Itraconazole, ketoconazole, and posaconazole
      ▪ Many of the Antiretroviral protease inhibitors
      ▪ Nefazodone
      ▪ Nicardipine
  – Strong 3A4 inducers

• Pharmacodynamic
  – Medications that increase the risk of bleeding
Drug Interaction Resources/References

- Lexi-Comp Interactions
- Micromedex Interactions
- Epic (FirstDatabank)
- Prescribing Information
- Literature search
- Pharmacist
Summary

• Drug interactions can occur with absorption, distribution, metabolism, and excretion.

• Phase I and Phase II reactions are key for the metabolism of medications.

• It is important to identify substrate (how it is metabolized and if a prodrug) and if any enzyme inducers or inhibitors will be given concurrently.

• Pharmacogenetics/genomics may play a role; however, need to consider the feasibility and do the results tell the entire story.

• Key tertiary references to evaluate drug interactions are Lexi-Comp Interactions and Micromedex.
Thank you for your time and attention