Cleveland Clinic

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 minimizes 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 interactons
  - 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.
  - **A**bsorption
  - **D**istribution
  - **M**etabolism
  - **E**xcretion/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) where as 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 anticoagulanta, 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 effects 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 patients 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, procainaminde, quinidine, cyclosporine (CSA), phenytoin, flecainide, mexilitine, 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 anitbiotics
    - 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 dagibatran.

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 erhythromycin

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

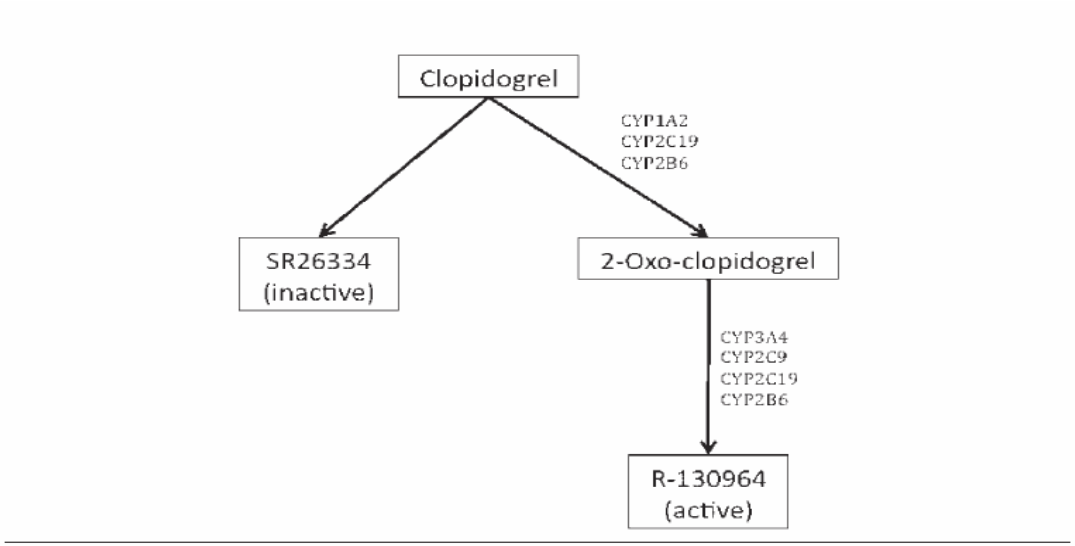

Figure 1. Metabolism of clopidogrel. Clopidogrel undergoes a 2-step metabolism and can involve several different cytochrome P450 enzymes.

Plavix ® (clopidogrel bisulfate) [package insert]. Bridgewater, NJ: Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership; August 2010.

Clopdiogrel

- Interaction with omeprazole and other PPIs has been controversial
- There is a know 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 Antiretoviral 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