CYP450 Cascade: Pharmacodynamic implications for contemporary practice

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Objectives

- At the conclusion of this presentation the attendee will:
  - Compare and contrast mechanisms of drug interactions.
  - Describe the CYP450 metabolism cascade.
  - Analyze a clinical example of a CYP450-mediated prescribing error.

Drug Interactions – Types

- Drug interactions occur in a variety of ways
  - Drug-food
  - Drug-herbal
  - Drug-disease
  - Drug-drug
    - Source- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm110632.htm#Preventing_Drug_Interactions, accessed 3.14.13.

Drug-food Interactions

- Mostly related to inhibition of absorption
- Risks related to decreased absorption of necessary therapeutic agents
  - Tetracycline and calcium products

Drug-herbal Interactions

- ASA, NSAIDs, platelet aggregate inhibitors, warfarin – Dong-quai and garlic, ginkgo
- St. John's wart – Antidepressants, indinavir, cyclosporine, digoxin

Drug-herbal Interactions (continued)

- Generally, patients should be cautious with herbal supplements if taking any of the following:
  - Blood pressure medications
  - Blood thinners (anticoagulants, anti-platelet agents, nonsteroidal anti-inflammatory drugs such as aspirin, ibuprofen or naproxen)

Drug-herbal Interactions (continued)

- Generally, patients should be cautious with herbal supplements if taking any of the following: (cont.)
  - Diabetes medications
  - Drugs that affect the liver
  - Cardiovascular medications

Drug-disease Interactions

- Liver disease- Decreased liver function may have significant impact on metabolism of drugs, producing both elevated or suppressed levels.

Drug-disease Interactions (continued)

- Renal disease often produces elevated levels of drugs requiring renal excretion of active metabolites.
- Therapeutic agents often exacerbate symptoms or progression of a co-morbid condition.

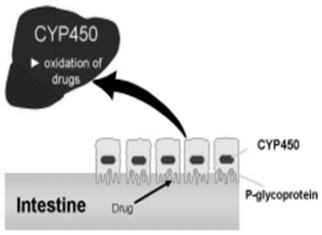
Drug-disease Interactions (continued)

- Liver disease and cephalosporins
- Renal disease and NSAIDs
- Therapeutic agents exacerbate another condition.
  - Thiazide diuretics and T2DM
  - Beta agonists and HTN
  - Steroids and osteoporosis
  - CCB and CHF
  - Lithium and hypothyroidism

Drug-drug Interactions

- Many drug-drug interactions related to the impact of one drug on the metabolism of another.
- CYP450 metabolism interactions implicated in a variety of well-known drug interactions.

First-pass metabolism and hepatic clearance



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CYP450 Drug Metabolism

- Most drugs are produced in a vehicle that has some degree of lipophilia.
- In order for drugs to be effective, they must be able to enter target cells.

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CYP450 Drug Metabolism (continued)

- Most are designed to be lipophilic so that they can penetrate the cell membrane and proceed to site of action.
- When the body perceives the introduction of an exogenous drug, its protective mechanisms immediately begin steps to eliminate it from the body.

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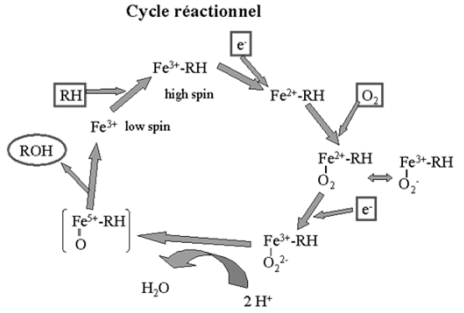
CYP450 Drug Metabolism (continued)

- In many cases this requires converting the drug from its lipophilic form to a hydrophilic form that can be excreted by the kidney.
- While there are other physiologic mechanisms that can convert drugs from lipophilic to hydrophilic, the majority are converted by the CYP450 enzyme cascade.

CYP450 Drug Metabolism (continued)

- The cascade is a series of oxidation-reduction reactions that result in a hydrophilic metabolite ready for excretion.
  - Source- Katzung, B.G. (2011). Basic and Clinical Pharmacology, (11th ed.). NY: McGaw-Hill Medical

CYP450 Cascade



CYP450 as a Mechanism for Drug-drug Interactions

- Numerous therapeutic agents are substrates of the CYP450 oxidation, reduction system.
- A variety of other therapeutic agents are either inhibitors or inducers of a CYP450 pathway.
- When inhibitors and substrates are given together, metabolism of the substrates is impaired, and toxic levels can occur.

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Commonly Encountered CYP450 Inhibitors (3A4,5,7)

- Amiodarone
- Cimetidine
- Ciprofloxacin
- Clarithromycin
- Diltiazem
- Erythromycin (E-mycin®)
- Fluconazole
- Fluvoxamine
- Grapefruit juice
- Itraconazole
- Ketoconazole
- Mifepristone
- Norfloxacin
- Norfluoxetine
- Verapamil

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Commonly Encountered CYP450 Substrates (3A4,5,7)

- Macrolide antibiotics
- Benzodiazepines
- HIV antivirals
- Prokinetics
- Antihistamines
- CCB
- Statins
- Steroid compounds
- Buspirone
- Caffeine and ergotamine (Cafergot®)
- Morphine
- Propranolol
- Sildenafil
- Zolpidem
- Lidocaine

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Commonly Encountered CYP450 Inhibitors (2D6)

- Amiodarone
- Bupropoin
- Chlorpromazine
- Cimetidine
- Citalopram
- Duloxetine
- Escitalopram
- Metoclopramide
- Paroxetine
- Quinidine
- Ranitidine
- Ritonavir
- Sertraline
- Terbinafine
- Ticlopidine
- H1RA

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Commonly Encountered CYP450 Substrates (2D6)

- Beta blockers
- TCAs
- Antipsychotics
- Antidysrhythmics
- Dextromethorphans
- SNRIs
- SSRIs

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Other CYP450 Subtypes

- CYP1A2
- CYP2C9
- CYP3C19
- CYP2E1
- Others exist
  - Known substrates, inhibitors and inducers not as commonly used

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Early Case Report
Healthy Young Adult

Syncope in a 39 Year-old Female

- A 39 year-old female, essentially healthy, being managed with terfenadine for allergies
- Treated with a 10-day course of cefaclor 250 mg TID for infection of the respiratory tract
- Presents for evaluation of a two-day history of syncope
  - Source- B. P. Monahan; C. L. Ferguson; E. S. Killeavy; B. K. Lloyd; J. Troy; L. R. Cantilena Jr. *JAMA;* 1990:2788-2900

Syncope in a 39 Year-old Female (continued)

- The patient was having episodes of Torsades de Points.
- Serum analysis revealed elevated levels of terfenadine and proportionately low levels of its metabolite.
- Upon interview the patient admitted self-medicating with ketoconazole 200 mg BID for vaginal yeast.
  - Source- B. P. Monahan; C. L. Ferguson; E. S. Killeavy; B. K. Lloyd; J. Troy; L. R. Cantilena Jr. *JAMA;* 1990:2788-290

Syncope in a 39 Year-old Female (continued)

- This was the first case of terfenadine-related cardio toxicity when used in prescribed doses.
- Terfenadine was taken off the US market several years later.
- Similar occurrences resulted in the removal of cisapride from the US market in 2000.
  - Source- B. P. Monahan; C. L. Ferguson; E. S. Killeavy; B. K. Lloyd; J. Troy; L. R. Cantilena Jr. *JAMA;* 1990:2788-290

Typical Outpatient Scenario

Clinical Presentation of a 61 Year-old Female with Dyslipidemia on Statin Monotherapy

Patient History

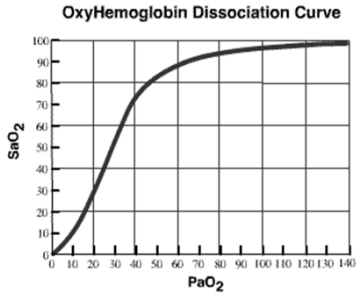
- Chief complaints
  - Subtle shortness of breath, pleuritic chest pain, worsening muscle weakness over the last week
  - Management of pneumonia (outpatient treatment failure)

Patient History (continued)

- History
  - 61 year-old female
  - Multiple chronic conditions are well-controlled
  - Dx with CAP and treated with clarithromycin 500 mg BID x 14 days
    - Improved, then symptoms returned

Physical Exam

- Physical exam
  - 61 year-old female in mild respiratory distress at rest; Ht: 5'4" (164.6 cm); Wt: 187 lbs (84.8 kg)
  - BP: 129/67 mm Hg, Pulse: 91 bpm, RR: 32 bpm
  - Temp: 99.2°F (37.3°C); SaO_2 (2L O_2) 93%



Medication History

- Lisinopril 40 mg QD
- Atorvastatin 80 mg QPM
- Levothyroxine 0.1 mg QD
- Beclomethasone nasal inhaler BID
- Doxazosin 4 mg QD
- Ibuprofen 400 mg PRN
- Clarithromycin 500 mg BID

Laboratory Values

- Past laboratory values (when dx'd with CAP)
  - Glucose: 85 mg/dL (4.7 mmol/L)
  - BUN: 23 mg/dL (8.2 mmol/L)
  - Cr: 1.2 mg/dL (106.1 µmol/L)
  - BUN/Cr: 19.2
  - Uric acid: 5.9 mg/dL (350.9 µmol/L)
  - Phos: 3.7 units/dL (1.2 mmol/L)
  - Calcium: 9.6 mg/dL (2.4 mmol/L)

Laboratory Values (continued)

- Past laboratory values (when dx'd with CAP) (cont.)
  - Total protein: 7.2 g/dL (72 g/L)
  - Albumin: 4.0 g/dL (40 g/L)
  - Globulin: 3.2 g/dL
  - Alk phos: 55 U/L
  - GGTP: 21 U/L
  - ALT/AST: 19/19 U/L
  - LDH: 125 U/L

Laboratory Values (continued)

- Past laboratory values (when dx'd with CAP) (cont.)
  - Na: 140 mg/dL
  - K: 4.0 mg/dL
  - Cl: 103 mg/dL
  - CO_2: 28 mg/dL A1c: 5.6% (.056 proportion)
  - TSH: 7.4 mIU/L

Laboratory Values (continued)

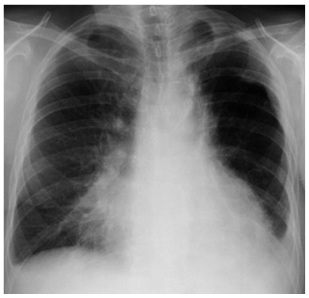
- Past laboratory values (when dx'd with CAP) (cont.)
  - WBC: 7.9 x 1000/cu mm
  - Hgb: 14.3 g/dL (143 g/L)
  - HCT: 42% (.42 proportion)
  - Plt: 304/mm^3
  - B_{12}: 404 pg/mL (298 pmol/L)
  - Cholesterol: 215 mg/dL (5.6 mmol/L)

Laboratory Values (continued)

- Past laboratory values (when dx'd with CAP) (cont.)
  - Triglycerides: 166 mg/dL (1.9 mmol/L)
  - HDL-C: 41 mg/dL (1.06 mmol/L)
  - VLDL: 33 mg/dL (.85 mmol/L)
  - Chol/HDL-C: 5.24 mg/dL (.14 mmol/L)
  - LDL-C: 141 mg/dL (3.65 mmol/L)

Radiograph and Diagnosis

- Chest radiograph
  - Right lobar consolidation with effusion
- Diagnosis
  - Pneumonia, outpatient treatment failure
- Treatment
  - IV extended spectrum penicillin



Laboratory Values (continued)

	Past	Current
ALT (7-56)	19 U/L	143 U/L
AST (5-40)	19 U/L	599 U/L
LDH (105-333)	125 U/L	961 U/L
CPK (22-198)	-	20,990 U/L
CR	1.2 mg/dL (106.1 µmol/L)	3.6 mg/dL (318.2 µmol/L)

Question

- The most significant finding in this patient is:
  - LDL-C of 141 mg/dL (3.65 mmol/L)
  - Low white count
  - Triglycerides of 166 mg/dL (1.9 mmol/L)
  - Muscle weakness

Question

- Risk factors for rhabdomyolysis in this patient include:
  - Combination of ibuprofen and atorvastatin.
  - Combination of clarithromycin and atorvastatin.
  - Combination of lisinopril and atorvastatin.
  - All of the above.

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Question

- Recommended treatment options for this patient include hydration and...
  - Treat elevated potassium.
  - Discontinue lovastatin.
  - Continue lovastatin in divided doses.
  - All of the above.

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Rhabdomyolysis in a 61 Year-old Female

- Case discussion
  - Presenting complaint: Muscle weakness
  - Initial LFTs: Normal
  - WBC: Low for pneumonia

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Rhabdomyolysis in a 61 Year-old Female (continued)

- Risk factors for rhabdomyolysis in this patient
  - Tx with medications associated with myopathy
    - Macrolide/HMG-CoA reductase inhibitor interaction
      - Clarithromycin/atorvastatin

Rhabdomyolysis in a 61 Year-old Female (continued)

- Risk factors for rhabdomyolysis in this patient (cont.)
  - High doses of HMG-CoA reductase inhibitors
    - Recommended atorvastatin dose: 10 to 80 mg daily
    - This patient received 80 mg QPM.

Where You'd Least Expect It

A 46 year-old male…

- …is admitted to the step down unit for management of altered mental status and depressed respirations
- His history is significant only for long-term chronic back pain managed with methadone

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A 46 year-old male… (continued)

- He was diagnosed with methadone toxicity
- The patient's methadone dose was stable and not recently changed
- It was determined that he did not purposefully or accidentally overdose

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A 46 year-old male… (continued)

- There were no new additions to his medication regiment recently
- His methadone was held for 3 days and he improved significantly
- A post-morbid analysis revealed that the only change in his circumstances was an attempt to quit smoking

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A 46 year-old male... (continued)

- Methadone is metabolized by both CYP3A4 and CYP1A2
- Certain hydrocarbons found in cigarette smoke are inducers of CYP1A2

A 46 year-old male... (continued)

- As the patient decreased his cigarette use he decreased induction of an isoenzyme that metabolizes methadone

Minimizing Drug Interactions

- Allergies
- Vitamins and herbs
- Old drugs and OTC
- Interactions
- Dependence
- Mendel (family history)

– Source- Centers for Research and Education on Therapeutics, USFDA, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm110632.htm#Preventing Drug Interactions, accessed 3.14.13.

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End of Presentation!

Thank you for your time and attention.

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