Making Sense of Cytochrome P450

Alan P. Agins, Ph.D.
President
PRN Associates, Ltd
Continuing Medical Education
Tucson, AZ

Objectives

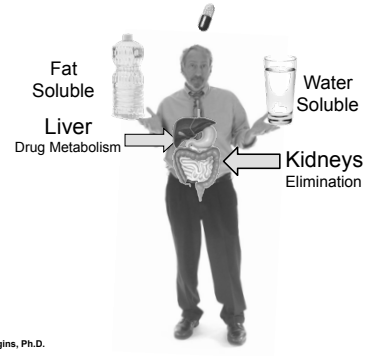
At the conclusion of this program, the participant will be able to:

- Define the physiological and pharmacological roles of cytochrome P450
- Describe the enzymatic process and clinical impact of cytochrome P450-dependent drug metabolism.
- List the major isoforms or subtypes of the cytochrome P450 enzymes that metabolize drugs
- Recognize the clinical ramifications of enzyme induction, inhibition and genetic polymorphism.

Cytochrome P450 Overview

Major drug metabolizing enzyme system in the body
Actually comprised of multiple proteins
Active site or core of the enzyme system is a heme protein
a.k.a. "mixed function monooxygenase"
Reactions require molecular oxygen
Liver and gut wall have the greatest concentration of P450
almost all tissues in body have some P450 (Lungs, Kidney, Skin, Brain)

Cytochrome P450: Raison d'etre



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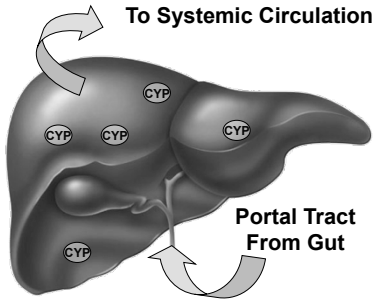
First Pass



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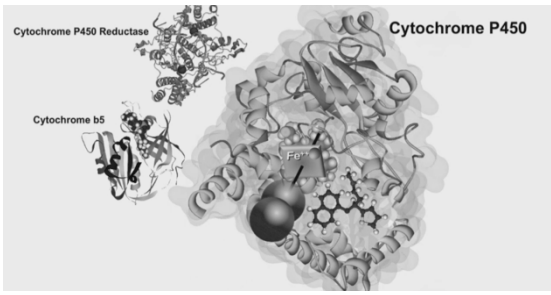
Cytochrome P450 Mechanism



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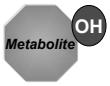
Fate of P450 Drug Metabolites



Inactive

Most drugs become inactive after P450 metabolism

Examples: warfarin, amlodpine, atorvastatin, lorazepam

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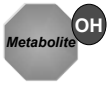
Fate of P450 Drug Metabolites

Equally Active

"Active Metabolite"



Examples:

fluoxetine → norfluoxetine
sildenafil → N-desmethylsildenafil
alprazolam → 4-hydroxyalprazolam

loratadine → desloratadine (Clarinex)
venlafaxine → O-desmethylvenlafaxine (Pristiq)
risperidone → 9-hydroxyrisperidone (Invega)

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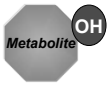
Fate of P450 Drug Metabolites



More Active

Examples:

losartan → E-3174 (10 – 40x)
tamoxifen → endoxifen
codeine → morphine

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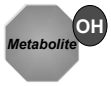
Fate of P450 Drug Metabolites



Activation of "ProDrug"

CYP450 necessary to convert drug to its active form

Examples:

clopidogrel → active compound
(ADP receptor blocker)

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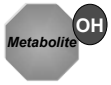
Fate of P450 Drug Metabolites



Reactive (Toxic) Metabolite

Examples:

acetaminophen → hepatotoxic metabolite
(N-acetyl-p-benzoquinone imine)

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You can know more than the Pharm Rep . . .

Why is it called Cytochrome P450?

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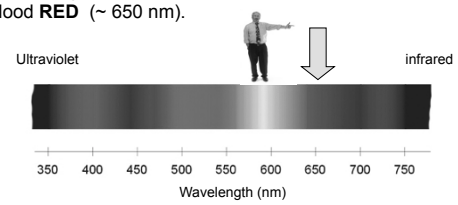
How Cytochrome P450 got its name

In hemoglobin, when the iron in the heme is reduced and binds to carbon monoxide (or oxygen) – the complex absorbs light in the visible spectrum such that it becomes blood **RED** (~ 650 nm).



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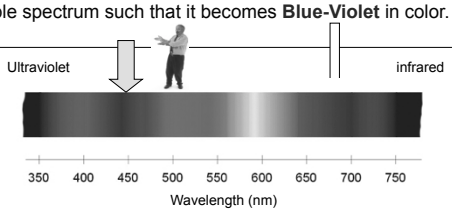
How Cytochrome P450 got its name

When liver drug metabolizing enzyme preparations are subjected to the same conditions (ie., reduced heme iron plus carbon monoxide) – the complex absorbs light in the visible spectrum such that it becomes **Blue-Violet** in color.



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Cytochrome P450

- **Humans have 17 families of CYP450 genes**
  - **39 subfamilies**
- **Three families dedicated to drug metabolism**
  - **CYPs 1, 2 and 3**
- **Remaining 14 families involved in physiological / homeostatic functions**
  - **biosynthesis or degradation of:**
    - **cholesterol**
    - **bile acids**
    - **steroid hormones**
    - **vitamin D3**

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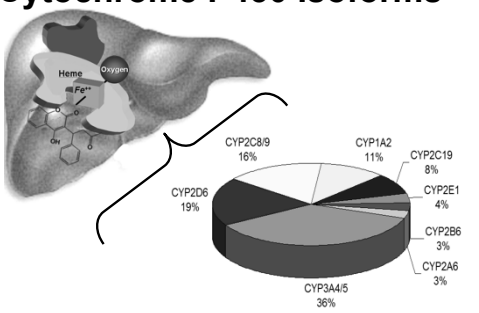
Cytochrome P450 Isoforms



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Some Drugs Metabolized by Cytochrome P450 CYP3A4

- Benzos: (alprazolam, diazepam, midazolam)
- Calcium Channel Blockers (all classes)
- Ethinyl Estradiol (and other synthetics)
- Opioids (fentanyl, methadone, oxycodone)
- oxybutynin / tolterodine
- Protease Inhibitors
- PDE-5 Inhibitors
- Statins (atorvastatin, lovastatin, simvastatin)
- carbamazepine
- (R)warfarin
- Buspirone
- Many others!

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Some Drugs Metabolized by Cytochrome P450 CYP2D6

- TCAs
- venlafaxine
- fluoxetine
- paroxetine
- haloperidol
- perphenazine
- Risperidone
- Atomoxetine
- Duloxetine
- Dextromethorphan
- Beta Blockers
  - Metoprolol
  - Carvedilol
  - Timolol
- Opioids
  - codeine
  - hydrocodone
  - tramadol
  - tapentadol

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Some Drugs Metabolized by Cytochrome P450

CYP2C19	CYP2C9	CYP1A2
clopidigrel	phenytoin	clozapine
PPIs	warfarin (S)	olanzapine
citalopram	losartan	tizanidine
escitalopram	valsartan	caffeine
diazepam	glipizide,	theophylline
voriconazole	glyburide	warfarin (R)
progesterone	rosiglitizone	duloxetine
	NSAIDs	ramelteon
	celecoxib	

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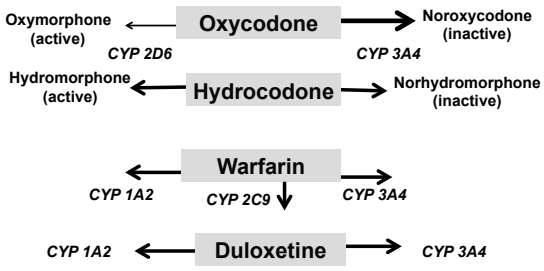
Some Drugs are metabolized by multiple CYP pathways



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Clinically Important Aspects of Cytochrome P450 Drug Metabolism

Induction

Elevated levels of Cytochrome P450

Inhibiton

Blockade of hepatic drug clearance

Pharmacogenetics

Variability between patients

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Induction

- reversible increase in enzyme concentration resulting from administration of certain drugs
- potential to increase rate of the "inducing" drug's breakdown
  "Pharmacokinetic or Drug Disposition Tolerance"
- may increase the metabolism of other drugs taken concurrently

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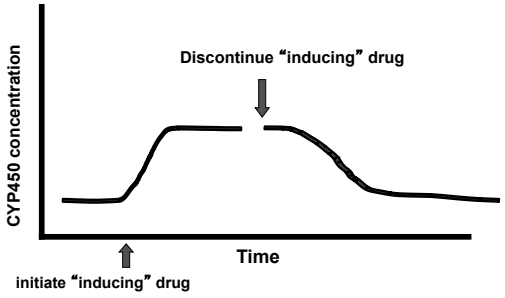
CYP450 Induction



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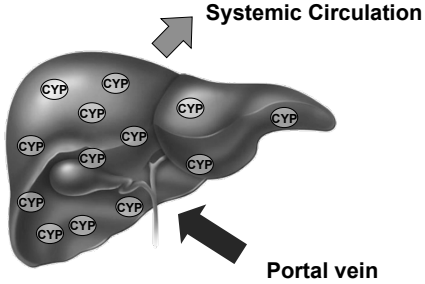
Induction



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CYP450 Induction

CYP 3A4

Interactions potentially leading to sub-therapeutic drug levels

Substrates

Calcium Channel Blockers
amlodipine, diltiazem, verapamil others
Statins
lovastatin, simvastatin, atorvastatin
Protease Inhibitors
Indinavir, nelfinavir, ritonavir, saquinavir
PDE5 Inhibitors
sildenafil, tadalafil, vardenafil
Benzodiazepines
alprazolam, midazolam, triazolam
Hypnotics
zolpidem, eszopiclone
Opioids
methadone, oxycodone, buprenorphine
Miscellaneous
buspirone
trazadone
estradiol, progesterone
ziprasidone
cyclosporine
warfarin (R)

Inducers

phenytoin
rifampin
carbamazepine
pioglitazone
efavirenz
nevirapine
St. John's wort

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CYP450 Induction

CYP1A2

Interactions potentially leading to sub-therapeutic drug levels

Substrates

Antipsychotics
clozapine,olanzapine

Antidepressants
duloxetine, mirtazapine, chlomipramine

Miscellaneous
frovatriptan
ropinirole
tizanidine
warfarin(R)
caffeine, theophylline

Inducers

rifampin
omeprazole
broccoli
brussel sprouts
cabbage
char-grilled meat
tobacco smoke

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CYP450 Induction

CYP2E1

Interactions potentially leading to **TOXICITY**

Substrates

Anesthetics
enflurane, halothane, isoflurane

Miscellaneous
acetaminophen
ethanol
isoniazid

Inducers

Ethyl alcohol
Whisky
Scotch
Bourbon
Vodka
Gin
Wine
Beer

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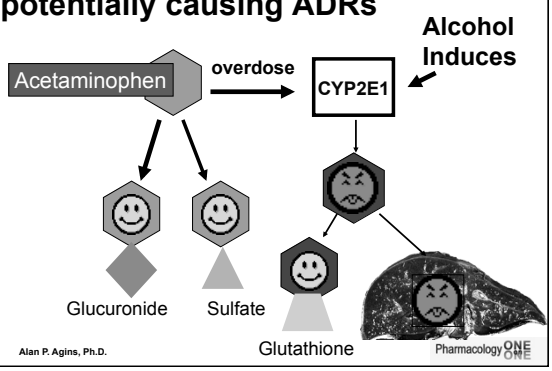
Induction – Interactions potentially causing ADRs



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Inhibition

- Due to two drugs competing for the same enzyme
- Drug with greater affinity typically wins!
- Some drugs get into active site and are slow to dissociate
- Drug that is not metabolized can build up to toxic levels

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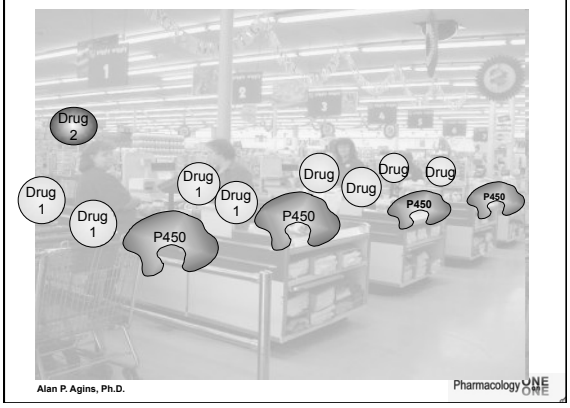

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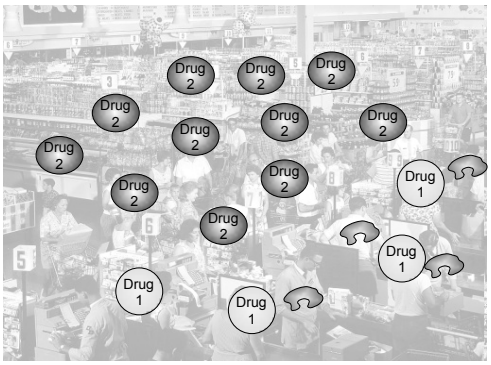

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CYP450 Inhibition

CYP3A4

Interactions potentially leading to **Toxic** drug levels

Substrates

Calcium Channel Blockers
amlodipine, diltiazem, verapamil others
Statins
lovastatin, simvastatin, atorvastatin
Protease Inhibitors
Indinavir, nelfinavir, ritonavir, saquinavir
PDE5 Inhibitors
sildenafil, tadalafil, vardenafil
Benzodiazepines
alprazolam, midazolam, triazolam
Hypnotics
zolpidem, eszopiclone
Opioids
methadone, oxycodone, buprenorphine
Miscellaneous
buspirone
trazadone
estradiol, progesterone
ziprasidone
cyclosporine
warfarin (R)

Inhibitors

clarithromycin
erythromycin
ketoconazole
itraconazole
fluconazole
ritonavir
verapamil
amiodarone
cyclosporine
furanocoumarins (grapefruit juice)

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The Grapefruit Juice Story

- Grapefruit juice contains dihydroxybergamottin - a "suicide" inhibitor of CYP3A4.
- It destroys some of the CYP3A4 in the small intestine, and the body must make new CYP3A4 to reestablish normal activity.
- The effect of grapefruit juice on CYP3A4 can last long after it passes through the small intestine and is eliminated from the body.
- Therefore: one cannot avoid the grapefruit juice ~ drug interactions by staggering juice consumption and drug administration.

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CYP450 Inhibition

CYP2D6

Interactions potentially leading to **Toxic** drug levels

Substrates

Antidepressants
fluoxetine, paroxetine, venlafaxine, duloxetine, amitriptyline, clomipramine, desipramine , imipramine,
Antipsychotics
risperidone, haloperidol, perphenazine
Beta Blockers
carvedilol, metoprolol, timolol
Opioids
tramadol,tapentadol, ***codeine***
Miscellaneous
atomoxetine
dextromethorphan
tamoxifen

Inhibitors

paroxitine
fluoxetine
bupropion
ritonavir
terbinafine
amiodarone
quinidine

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CYP450 Inhibition

CYP2D6

Interactions potentially leading to **Sub-therapeutic** drug levels

Substrates

Pro-drug Substrates
(need activation by CYP2D6)

codeine
diminished analgesia

tamoxifen
decreased protection

Inhibitors

paroxitine
fluoxetine
bupropion
ritonavir
terbinafine
amiodarone
quinidine

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CYP450 Inhibition

CYP2C9

Interactions potentially leading to **Toxic** drug levels

Substrates

Miscellaneous
phenytoin
warfarin(S)
sulfamethoxazole

NSAIDs
diclofenac, ibuprofen, meloxicam, naproxen

Oral Hypoglycemic Agents
glyburide, glipizide, glimepiride

Angiotensin II Blockers
losartan, irbesartan, valsartan, candesartan

Inhibitors

fluconazole
amiodarone
ketoconazole
voriconazole
miconazole
sulfamethoxazole
gemfibrozil

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CYP450 Inhibition

CYP2C19

Interactions potentially leading to **Toxic** drug levels

Substrates

PPIs
lansoprazole, omeprazole, esomeprazole pantoprazole, rabeprazole

Miscellaneous
clopidogrel
citalopram
escitalopram
phenytoin
warfarin (R)
voriconazole

Inhibitors

omeprazole
esomeprazole
lansoprazole
pantoprazole
rabeprazole
cimetidine
fluoxetine
ketoconazole

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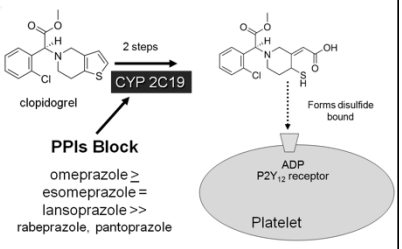
CYP450 Inhibition

CYP2C19

Interactions potentially leading to **Sub-therapeutic** drug levels



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CYP450 Inhibition

CYP1A2

Interactions potentially leading to **Toxic** drug levels

Substrates

Antipsychotics
clozapine, olanzapine

Antidepressants
duloxetine, mirtazapine, chlomipramine

Miscellaneous
frovatriptan
ropinirole
tizanidine
warfarin(R)
caffeine, theophylline

Inhibitors

fluvoxamine
ciprofloxacin
cimetidine

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Pharmacogenetics & Cytochrome P450

Major P450 Isoforms

- **CYP3A4**
- **CYP2D6 - Polymorphism**
- **CYP2C19 - Polymorphism**
- **CYP2C9 - Polymorphism**
- **CYP1A2**
- **CYP2E1**

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CYP2D6 Poor Metabolizers (PM)

- Inheritance of two mutant *CYP2D6* alleles
- No enzyme or very poor enzyme activity = impaired metabolism of CYP2D6 substrates

Caucasians	**8 – 14%**
African-Americans	**2 – 4 %**
Japanese / Chinese	**< 1%**

Higher plasma drug level due to decreased drug clearance; exaggerated clinical outcome and increased risk of dose-dependent side effects; may have to lower drug dose

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Drugs Metabolized by CYP2D6
Potential Consequences in PMs

- TCAs
- venlafaxine
- fluoxetine
- paroxetine
- haloperidol
- perphenazine
- risperidone
- atomoxetine
- tamoxifen

– dextromethorphan
– Beta Blockers
  - metoprolol
  - carvedilol
– Opioids
  - **codeine**
  - hydrocodone
  - oxycodone
  - tramadol

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CYP2D6
Ultra-extensive Metabolizers (UEM)

- Inheritance of alleles with duplication or amplification of *CYP2D6* genes
- Excessive amount of enzyme expressed, high metabolic capacity

Northern Africans Eastern Africans Saudi Arabians	10 - 30 %
Spaniards	3.5%
Zimbabweans	2.0%
Germans	1.8%
Chinese	1.3%

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Drugs Metabolized by CYP2D6
Potential Consequences in UEMs

- TCAs
- venlafaxine
- fluoxetine
- paroxetine
- haloperidol
- perphenazine
- **risperidone**
- atomoxetine
- tamoxifen
- – dextromethorphan
- – Beta Blockers
  - metoprolol
  - carvedilol
- – Opioids
  - **codeine**
  - hydrocodone
  - oxycodone
  - tramadol

Possibly higher than normal drug dose required for efficacy; side effects if metabolites are toxic

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Cytochrome P450
CYP2C19 Polymorphism

- Poor Metabolizers
  - – 25% Caucasian
  - – 30% African American
  - – 40% to 50% Asian
  - – May affect clearance of:
  - – amitriptyline, clomipramine, **phenytoin**, ***progesterone***, propranolol, **PPIs** (lansoprazole, omeprazole, pantoprazole, rabeprazole, etc), warfarin
- **May impact effectiveness of Plavix**

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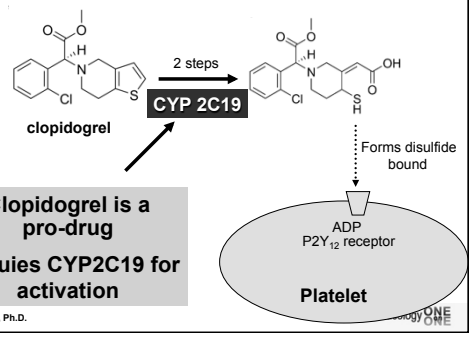
Polymorphisms leading to Black Boxed Warning on Plavix — CYP2C19



Clopidogrel is a pro-drug

Requies CYP2C19 for activation

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Cytochrome P450 CYP2C9 Polymorphism

- More than 50 SNPs have been described in the regulatory and coding regions of the CYP2C9 gene
- Some of them are associated with reduced enzyme activity
- 10–35% of Caucasians are poor metabolizers
- May affect clearance of:
  - **Phenytoin, *S-warfarin***
  - losartan, valsartan, glipizide, glyburide, NSAIDs, celecoxib, rosuvastatin, fluvastatin

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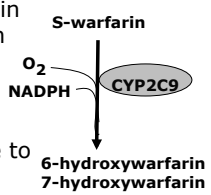
Warfarin and Genetic Variability – Cytochrome P450 CYP2C9

- Polymorphism of CYP2C9 in ~ 10 – 35 % of Caucasian
  - very rare in African-American or Asian populations
  - Does not influence time to reach effective INR
    - (as opposed to VKORC1)
  - Shortens time to INR > 4.



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Summary of non-polymorphism factors that may affect Cytochrome P450

- Alcohol
- Other drugs
- Caffeine
- Constituents of tobacco
- Char-broiled foods
- Cruciferous vegetables
- Grapefruit juice
- Air or water pollutants

- Induction or Inhibition

- More likely to affect
  - CYP3A4
  - CYP1A2
  - CYP2E1

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Other factors that may affect Cytochrome P450 metabolism

Age - Pediatric *vs* Adult *vs* Geriatric -

Infants do not develop a mature enzyme system until more than 2 weeks after birth.

Both quantitative & qualitative difference in pediatrics (neonates, infants, puberty)

Elderly have age related decreases in liver mass, hepatic enzyme activity and hepatic blood flow.

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Other factors that may affect Cytochrome P450 metabolism

Gender

Steroid induction of CYP3A may be responsible for some of the pharmacokinetic differences between men and women

Also within an individual over his/her life cycle from the prepubertal years to puberty and on through menopause

Liver Health

Hepatic disease (ie., hepatitis, cirrhosis, etc.) will result in impaired metabolism of drugs by Cytochrome P450

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Summary

Cytochrome P450 plays a critical role in both physiological and pharmacological processes.

It is important to recognize the clinical ramifications of induction, inhibition and genetics for drugs cleared through the CYP450 system.

Cytochrome P450-related metabolism is one of the major sources of drug interactions

Due to genetic polymorphism, it may be advantageous to include a family med history when taking the pts

In addtion to drugs, P450 activity can be influenced by age, liver status, dietary and lifestyle habits

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Questions?

Thanks for listening.

Alan

Web: www.gotpharm.com
www.Pharm1on1.com

Email: aagins@gotpharm.com

Facebook: / gotPharm

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