What Did They do to Us!?

UNDERSTANDING PHARMACOKINETICS, PHARMACODYNAMICS AND DRUG-DRUG INTERACTIONS

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Name	Role	Relationship	Company
Chloé LeBegue-Polley	Consultant	Owner	CLP Consulting, LLC
Chloé LeBegue-Polley	Joint Patent Holder	Patent Holder	University of South Carolina-Live Biotherapeutics

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Activity Code (Part 1)

Activity Code: **150957**

Instructions for claiming credits/contact hours can be found here.

Objectives

Part 1:

1. Differentiate between pharmacokinetics and pharmacodynamics
2. Understand common pathways for drug-drug interactions

Part 2:

1. Learn how to utilize high quality drug-drug interaction resources
2. Identify drug-drug interactions common in the oncology setting
3. Patient case

Medication Regimens: Rarely Perfect, Likely Complicated

Protocolspeak: Learn the Language

- Pharmacokinetics (PK)
  - The dynamics of drug absorption, distribution, metabolism, and elimination (ADME)
  - What the BODY does to the DRUG
- Pharmacodynamics (PD)
  - The study of the biochemical and physiological effects of drugs and their mechanisms of action
  - What the DRUG does to the BODY

Hilal-Dandan R, Brunton LL. eds. *Goodman and Gilman's Manual of Pharmacology and Therapeutics, 2e*. McGraw Hill; 2016. Accessed January 15, 2024. https://hemonc-mhmedical-com.proxy1.library.virginia.edu/content.aspx?bookid=1810&sectionid=123789184

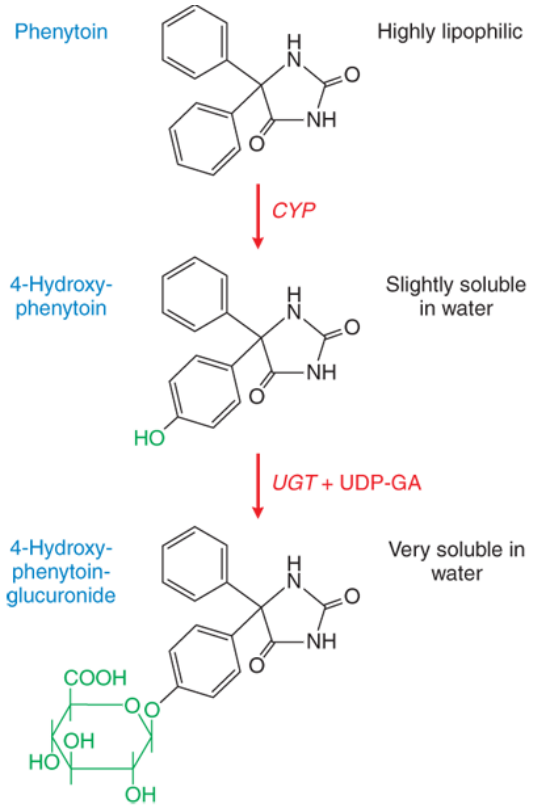
Pharmacokinetics: ADME

- Absorption
  - The movement of a drug from its site of administration into the central compartment
  - *Bioavailability* describes the fractional extent to which a dose of drug reaches its site of action
  - IV medications bypass this process (more dangerous!)
- Distribution
  - Movement of drug into interstitial and intracellular fluids depending on the particular physicochemical properties of the individual drug
  - *Volume of distribution* is the fluid volume that would be required to contain all of the drug in the body at the same concentration measured in the blood or plasma
  - Think about this as "Where does the drug like to go in the body?"
    - Hydrophilic characteristics vs. hydrophobic
    - Certain medications "prefer" adipose tissue, etc

Hilal-Dandan R, Brunton LL. eds. *Goodman and Gilman's Manual of Pharmacology and Therapeutics, 2e*. McGraw Hill; 2016. Accessed January 15, 2024. https://hemonc-mhmedical-com.proxy1.library.virginia.edu/content.aspx?bookid=1810&sectionid=123789184

Pharmacokinetics: ADME

- Metabolism
  - Biotransformation of drug into metabolites
  - Preparation of molecule to exit the body
  - Not all drugs are metabolized; some are excreted unchanged
  - Prodrugs are metabolized into active agents
- Excretion
  - Clearance
  - Elimination of the drug from the body either unchanged or as metabolites
    - Renal
    - Biliary
    - Fecal
    - Via sweat/saliva/tears/breath



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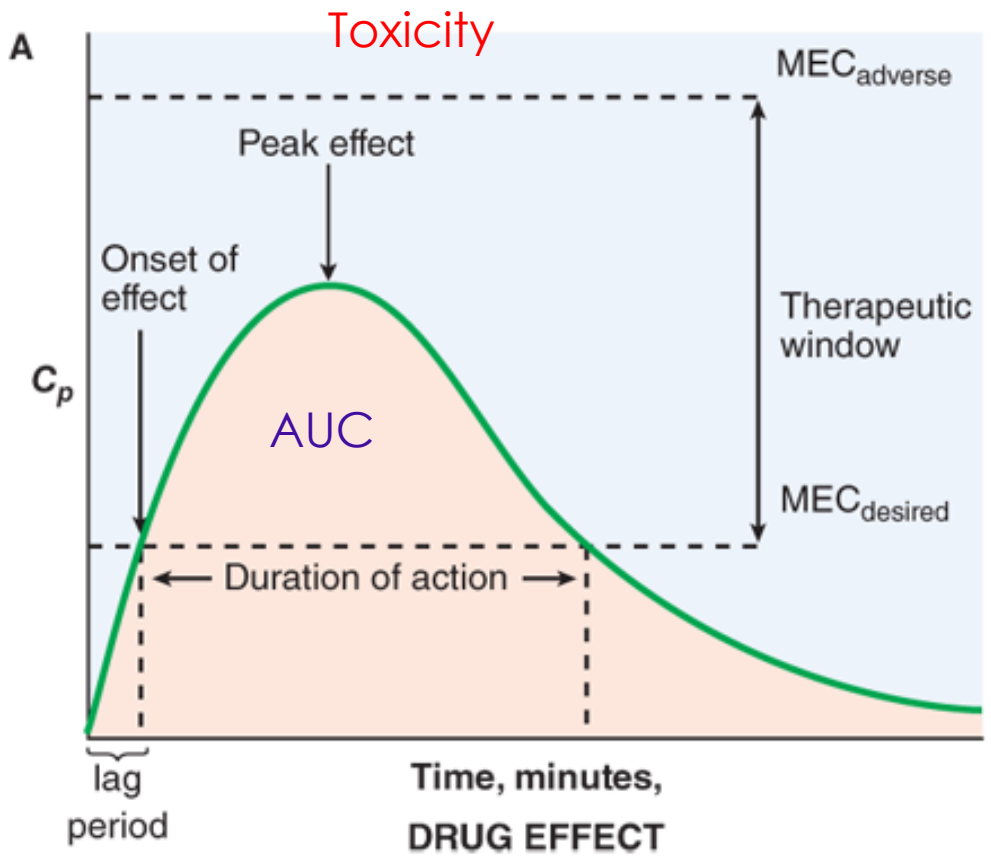
Pharmacokinetics and Drug Efficacy



MEC: Minimum Effective Concentration

Drug is effective ONLY in the therapeutic window

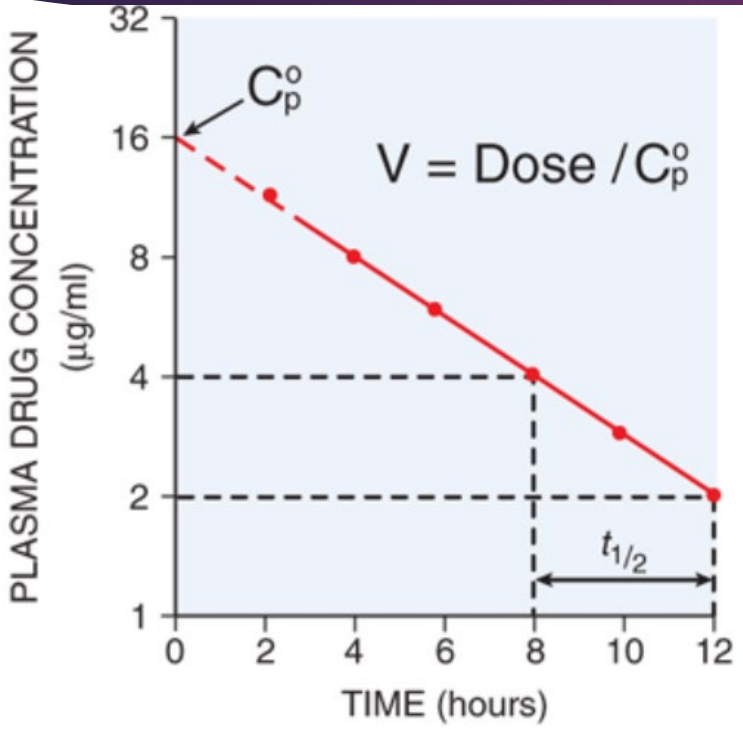
AUC: Area Under Curve

Drug under MEC is in the system, but not effective

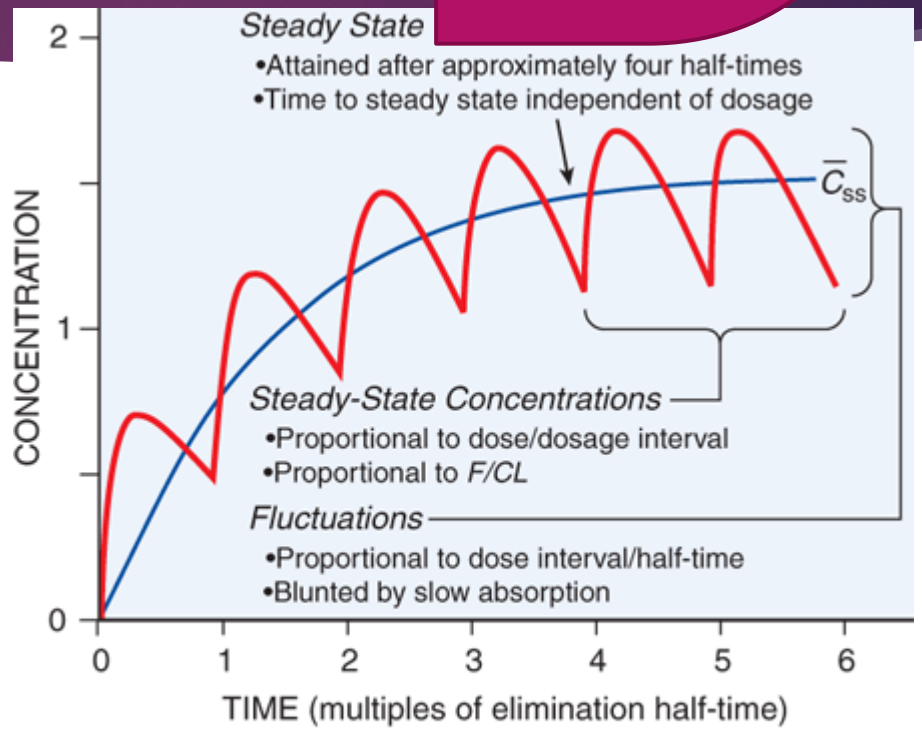
Buxton IO. Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, Metabolism, and Elimination. In: Brunton LL, Knollmann BC. eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14th Edition*. McGraw-Hill Education; 2023. Accessed February 23, 2024. https://hemonc-mhmedical-com.proxy1.library.virginia.edu/content.aspx?bookid=3191&sectionid=267905627

Metabolism Visualized

SS: In = Out



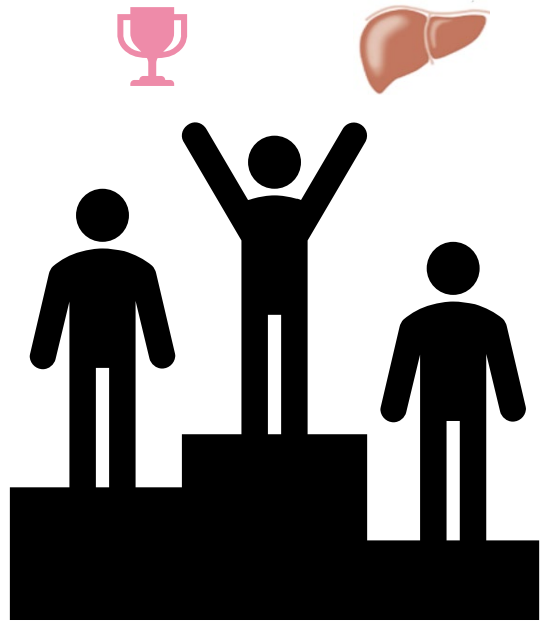
Source: Randa Hilal-Dandan, Laurence L. Brunton: Goodman and Gilman's Manual of Pharmacology and Therapeutics, 2nd Edition, www.accesspharmacy.com



Source: Randa Hilal-Dandan, Laurence L. Brunton: Goodman and Gilman's Manual of Pharmacology and Therapeutics, 2nd Edition, www.accesspharmacy.com

Where does metabolism occur?

- Liver
  - Primary site of biotransformation
  - The powerhouse of metabolism
  - First pass metabolism
- GI Tract
- Kidneys
- Lungs and nasal mucosa (aerosols)



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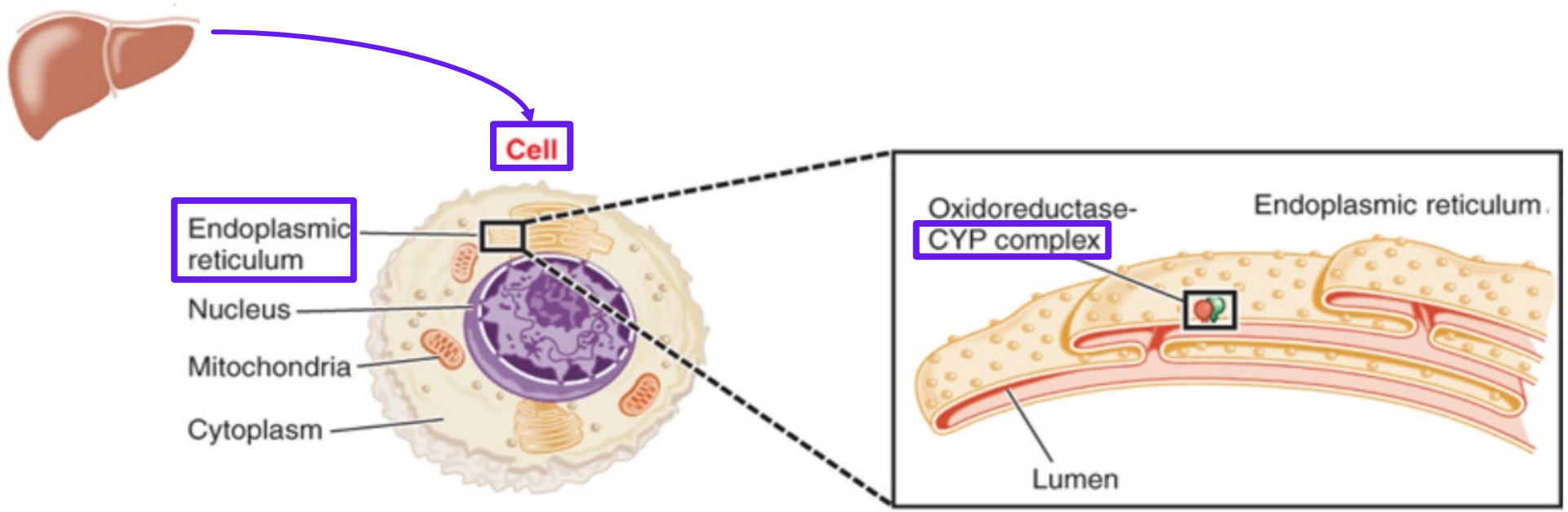
Where does metabolism occur?



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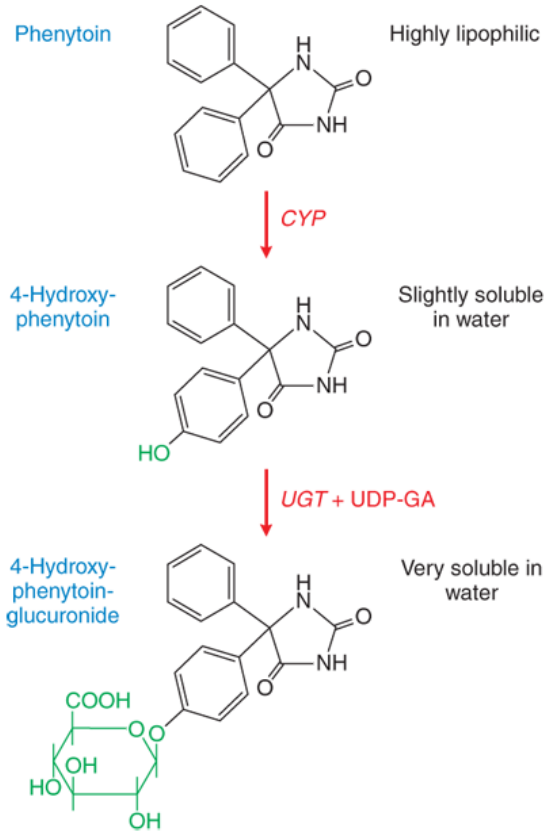
Metabolism: Two Phase Process

- Phase 1: Biological Inactivation

Turn it OFF

- Phase 2: Further metabolism of Phase 1 Metabolite

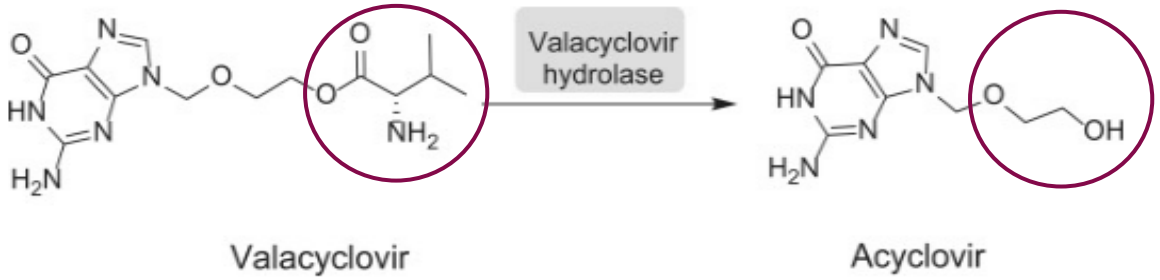
Get it OUT



Source: Randa Hilal-Dandan, Laurence L. Brunton: Goodman and Gilman's Manual of Pharmacology and Therapeutics, 2nd Edition, www.accesspharmacy.com

Prodrugs

- Pharmacologically inactive compounds that are converted to their active forms by metabolism
- This can maximize the amount of the active metabolite that reaches its site of action
- Valacyclovir (prodrug) → Acyclovir (active metabolite, antiviral)



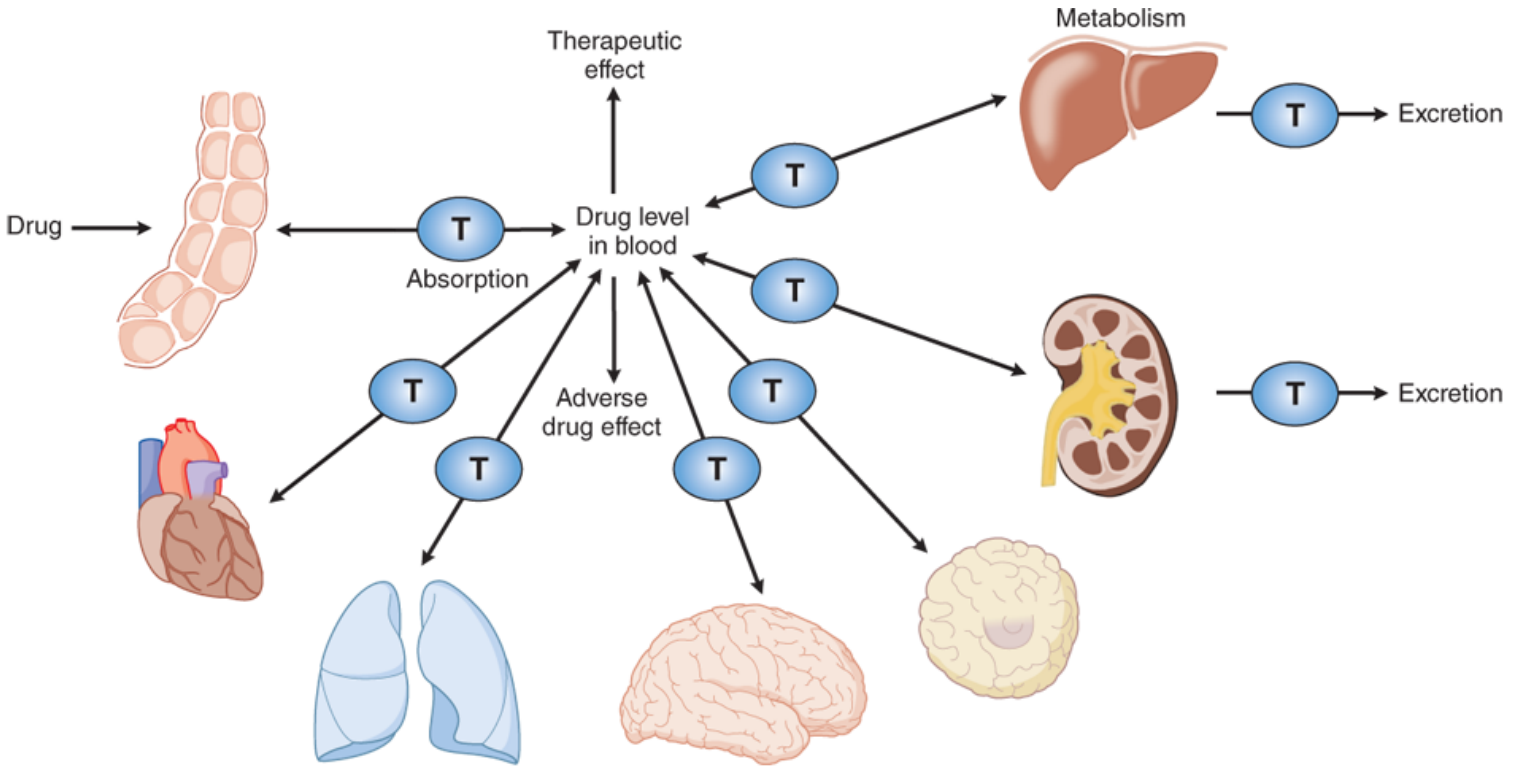
Buxton IO. Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, Metabolism, and Elimination. In: Brunton LL, Knollmann BC. eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14th Edition. McGraw-Hill Education; 2023. Accessed February 23, 2024. https://hemonc-mhmedical-com.proxy1.library.virginia.edu/content.aspx?bookid=3191&sectionid=267905627 Image: Devendra Choudhary, ... Rakesh K. Tekade, in The Future of Pharmaceutical Product Development and

Drug Transport Proteins

- Proteins which control the influx of essential nutrients and ions and the efflux of cellular waste, environmental toxins, drugs, and other xenobiotics
- Mediate tissue-specific drug distribution (drug targeting)
- Serve as protective barriers (ex: blood brain barrier)
- Transporters that are involved in pharmacokinetics are primarily located in intestinal, renal, and hepatic epithelia
  - Absorption and elimination of xenobiotics
  - Work together with drug-metabolizing enzymes to eliminate drugs and their metabolites

Giacomini KM, Sugiyama Y. Membrane Transporters and Drug Response. In: Brunton LL, Knollmann BC. eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14th Edition*. McGraw-Hill Education; 2023. Accessed February 23, 2024. https://hemonc-mhmedical-com.proxy1.library.virginia.edu/content.aspx?bookid=3191&sectionid=267774770

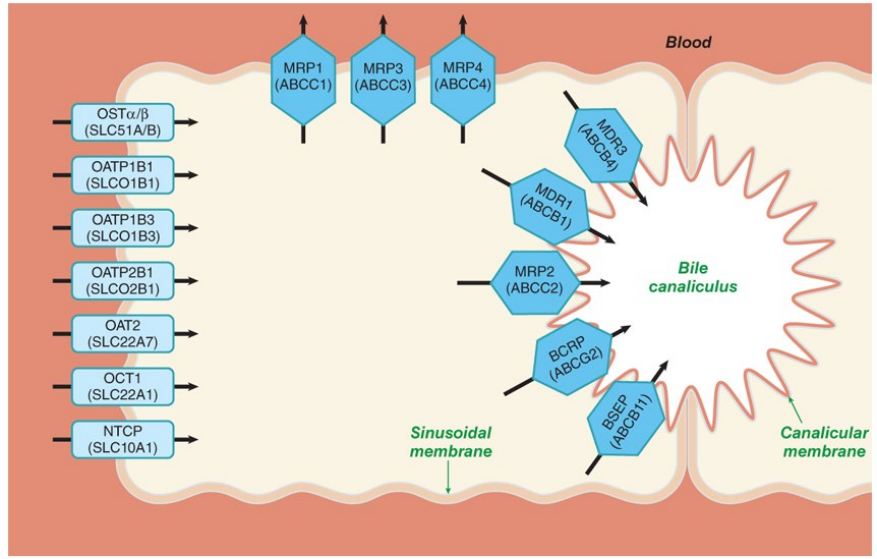
Drug Transport Proteins



Source: Laurence L. Brunton, Björn C. Knollmann:
Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14e:

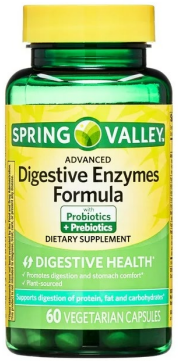
Drug Transport Proteins

- ABC and SLC transporter families
- Hepatic uptake is mediated by SLC-type transporters in the membrane of hepatocytes: OATPs (SLCO)/OAT2 (SLC22A7), OCTs (SLC22), and NTCP (SLC10A1)
- ABC transporters such as MRP2, MDR1, BCRP, BSEP, and MDR3 in the membrane of hepatocytes mediate the efflux of drugs and their metabolites



Giacomini KM, Sugiyama Y. Membrane Transporters and Drug Response. In: Brunton LL, Knollmann BC. eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14th Edition*. McGraw-Hill Education; 2023. Accessed February 23, 2024. https://hemonc-mhmedical-com.proxy1.library.virginia.edu/content.aspx?bookid=3191&sectionid=267774770

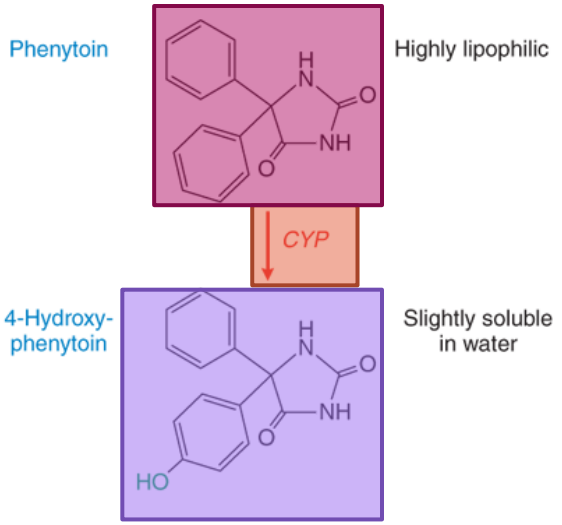
Q: What do these products have in common?



Images retrieved from public domain

A: Enzymagic! (Enzyme Magic)

- Enzyme
  - A catalyst of high molecular weight and biological origin
  - Catalyze the chemical reactions that make life possible
  - Nearly all enzymes are proteins
  - Many pathologies are the direct consequence of issues with key enzymes
- Substrate
  - Enzymes that catalyze the conversion of one or more compounds (*substrates*) into one or more different compounds (*products*)



Kennelly PJ, Rodwell VW. Enzymes: Mechanism of Action. In: Kennelly PJ, Botham KM, McGuinness OP, Rodwell VW, Weil P. eds. *Harper's Illustrated Biochemistry, 32nd Edition*. McGraw Hill Education; 2023. Accessed January 16, 2024. https://accessmedicine-mhmedical-com.proxy1.library.virginia.edu/content.aspx?bookid=3220&sectionid=268300507

Enzyme Families

- Cytochrome P450 (CYP) Superfamily
  - CYPs that carry out xenobiotic metabolism can metabolize structurally diverse chemicals
    - Xenobiotic: chemical from outside the body that ended up in the body
  - CYPs are promiscuous in their capacity to bind and metabolize multiple substrates
    - This both good and bad
  - Extensive overlapping substrate specificities by the CYPs is one of the underlying reasons for the predominance of drug-drug interactions
    - Competition for binding site

Hilal-Dandan R, Brunton LL. eds. *Goodman and Gilman's Manual of Pharmacology and Therapeutics, 2e*. McGraw Hill; 2016. Accessed January 15, 2024. https://hemonc-mhmedical-com.proxy1.library.virginia.edu/content.aspx?bookid=1810&sectionid=123789184

CYP Nomenclature

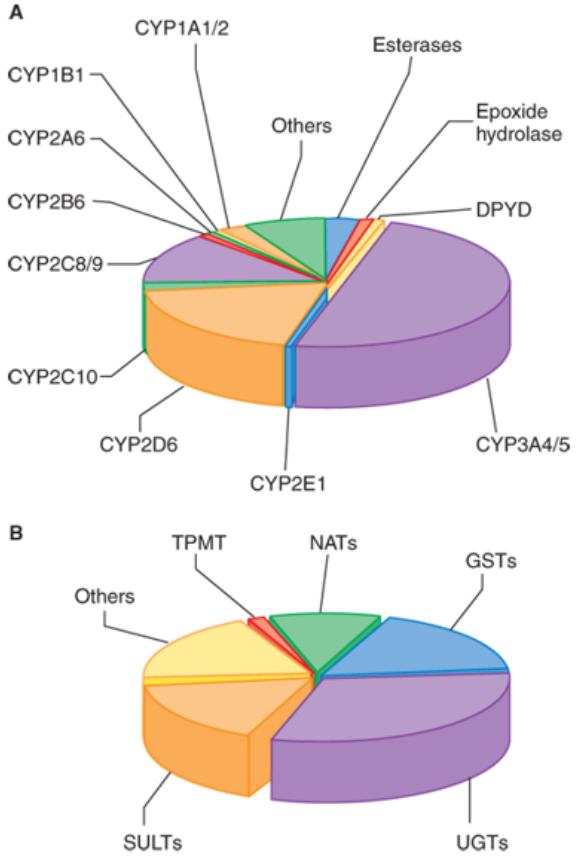
- Named from encoding gene
- Grouped based on amino acid sequence similarity
- Root CYP → Family (#) → Subfamily (Letter) → Form (#)
- CYP3A4 is family 3, subfamily A, gene number 4

CYP3A4

Hilal-Dandan R, Brunton LL. eds. *Goodman and Gilman's Manual of Pharmacology and Therapeutics, 2e*. McGraw Hill; 2016. Accessed January 15, 2024. https://hemonc-mhmedical-com.proxy1.library.virginia.edu/content.aspx?bookid=1810&sectionid=123789184

CYPs to Know and Love

- About 12 CYPs are responsible for metabolism of most xenobiotics
  - CYP1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, **3A4**, and **3A5**
- CYP3A4 is involved in the metabolism of over 50% of clinically used drugs
  - Most abundantly expressed in the liver
- Estimated Percentage of Utilization
  - Phase 1 (Image A)
  - Phase 2 (Image B)



Source: Randa Hilal-Dandan, Laurence L. Brunton: Goodman and Gilman's Manual of Pharmacology and Therapeutics, 2nd Edition, www.accesspharmacy.com

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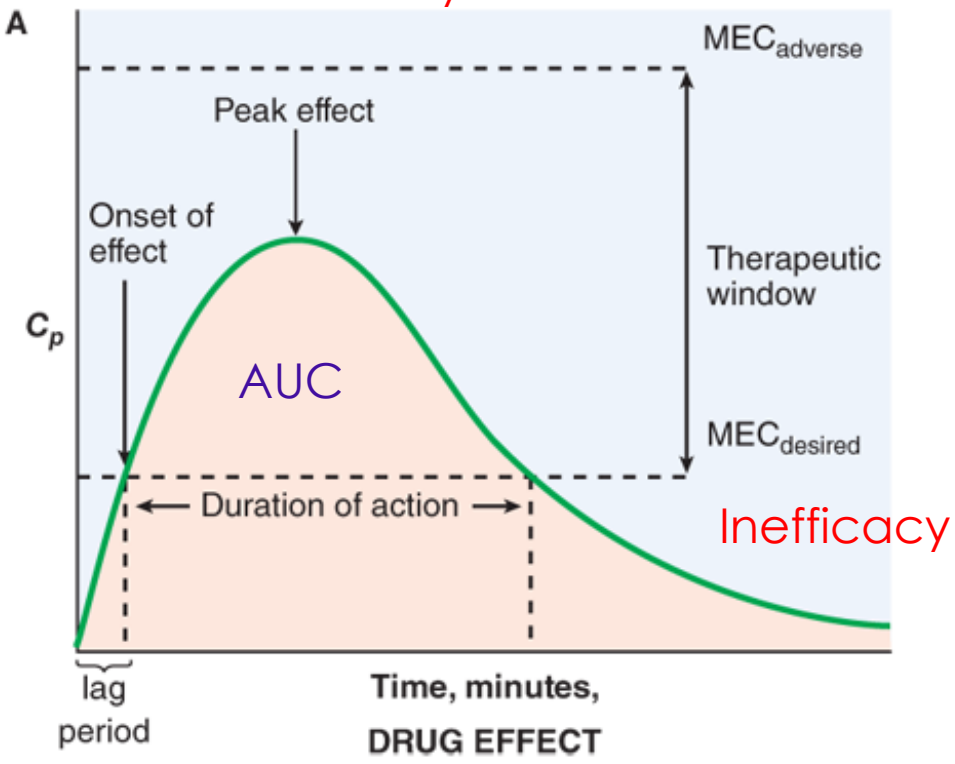
Mechanisms of DDI

- One drug causes another drug to be **metabolized too quickly**, losing therapeutic efficacy
- One drug causes another drug to be **metabolized too slowly**, causing accumulation and toxicity
- One drug causes another drug to **not be absorbed**, preventing therapeutic efficacy
- A drug may **change transcription and expression of genes** encoding drug-metabolizing enzymes

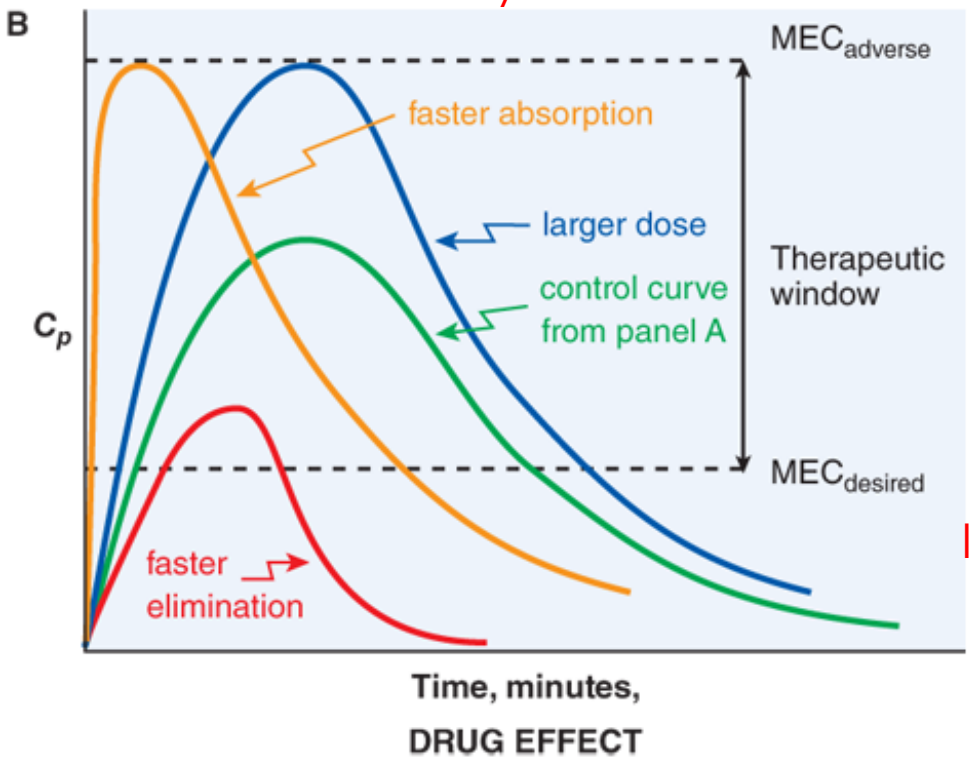
Hilal-Dandan R, Brunton LL. eds. *Goodman and Gilman's Manual of Pharmacology and Therapeutics, 2e*. McGraw Hill; 2016. Accessed January 15, 2024. https://hemonc-mhmedical-com.proxy1.library.virginia.edu/content.aspx?bookid=1810&sectionid=123789184

DDI Pharmacokinetics

Toxicity



Toxicity



Drug-Drug Interaction Players

Perpetrator

- Inhibits or induces drug metabolism by a given pathway
- Ex. CYP3A Strong Index Inhibitors
  - Clarithromycin
  - Itraconazole
- Ex. Of CYP3A Strong Index Inducers
  - Carbamazepine
  - Phenytoin
  - Rifampin

Victim

- Substrate and victim are used interchangeably
- Refers to the drug whose exposure may or may not be changed by a perpetrator drug in clinical DDI studies
- Ex. Of CYP3A Clinical Index Substrates
  - Midazolam
  - Triazolam

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) *Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry* FDA; January 2020. Accessed January 18, 2024. https://www.fda.gov/media/134581/download and related tables: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

Consequences of DDI

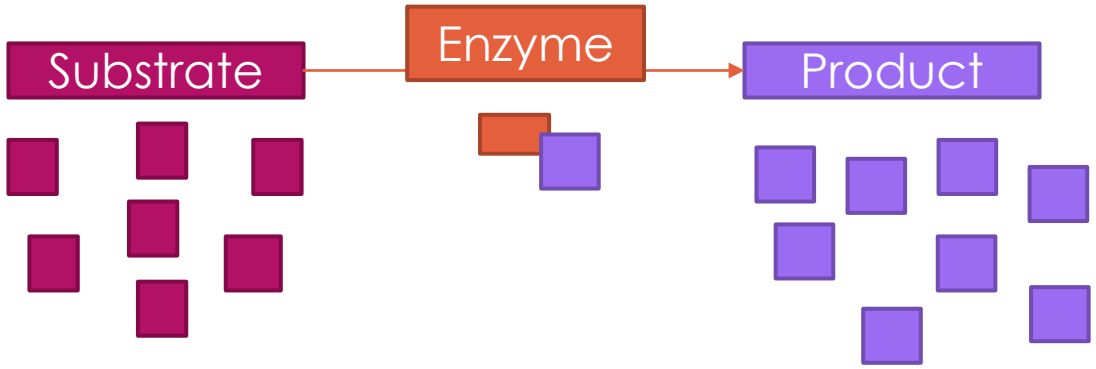
- Synergistic Effect
  - Enhanced efficacy
  - Two agents work together to enhance a given effect
- Antagonistic Effect
  - Decreased efficacy
  - One drug cancels the effect of the other
- Increased Adverse Events
  - Off-target effects

FDA Definitions – Substrate (Victim)

Substrate Category	
Sensitive Substrate	Drugs that demonstrate an increase in AUC of ≥5-fold with strong inhibitors of a given metabolic pathway
Moderate Sensitive Substrate	Drugs that demonstrate an increase in AUC of ≥2 to <5-fold with strong inhibitors of a given metabolic pathway
AUC: Area Under Curve	

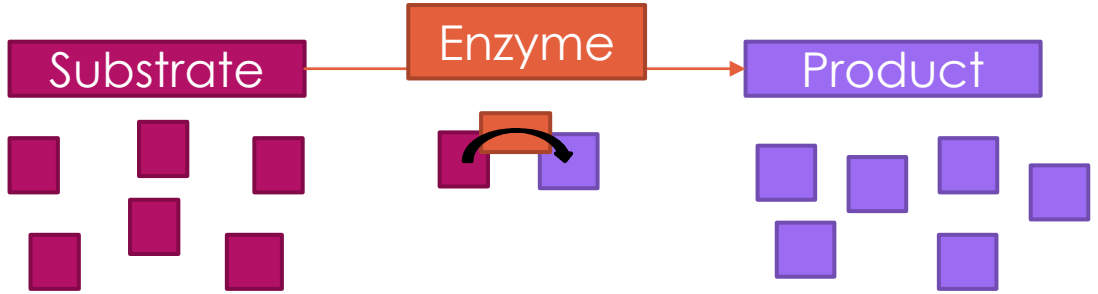
For Healthcare Professionals | FDA's Examples of Drugs that Interact with CYP Enzymes and Transporter Systems https://www.fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems Accessed 15 JAN 2024

Enzymatic Biotransformation

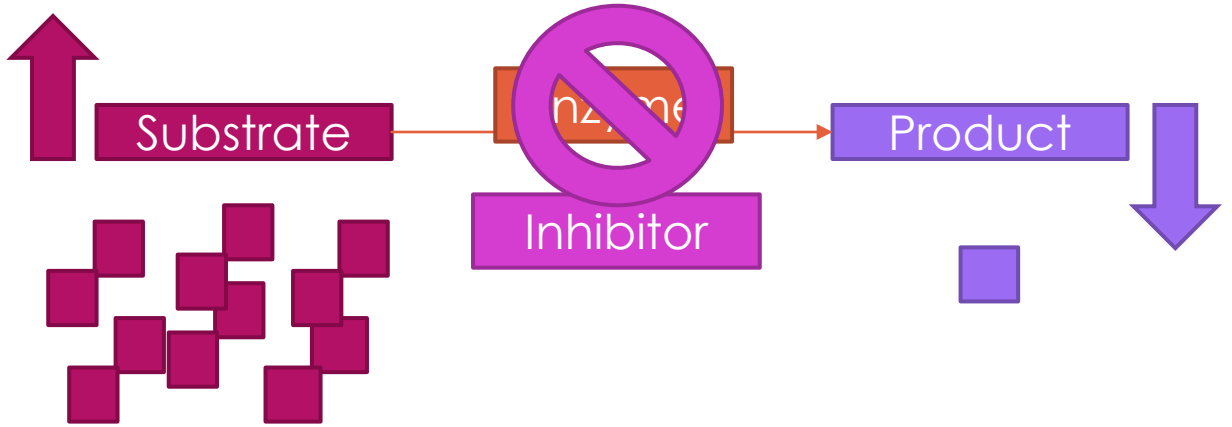


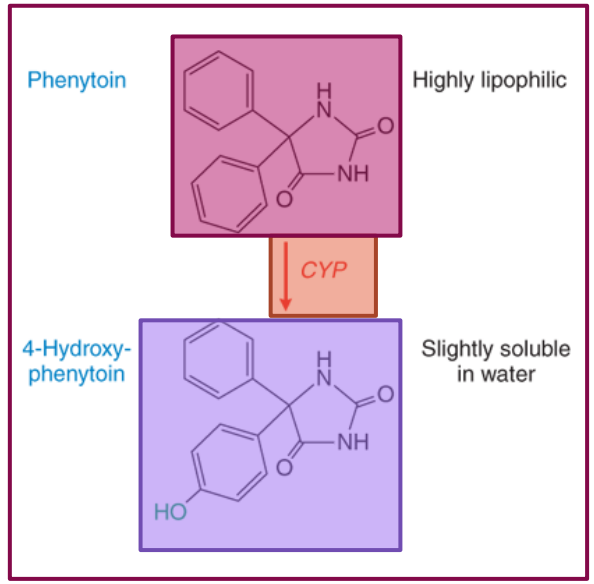
Inhibitor vs. Inducer

Normal Enzymatic Biotransformation



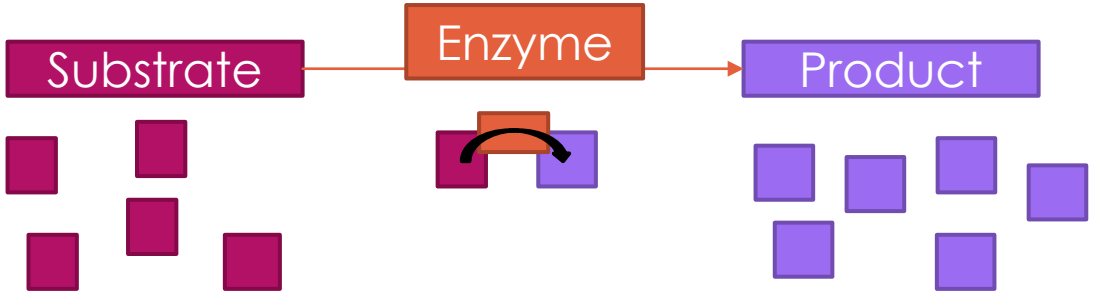
Biotransformation with Introduction of **Inhibitor**



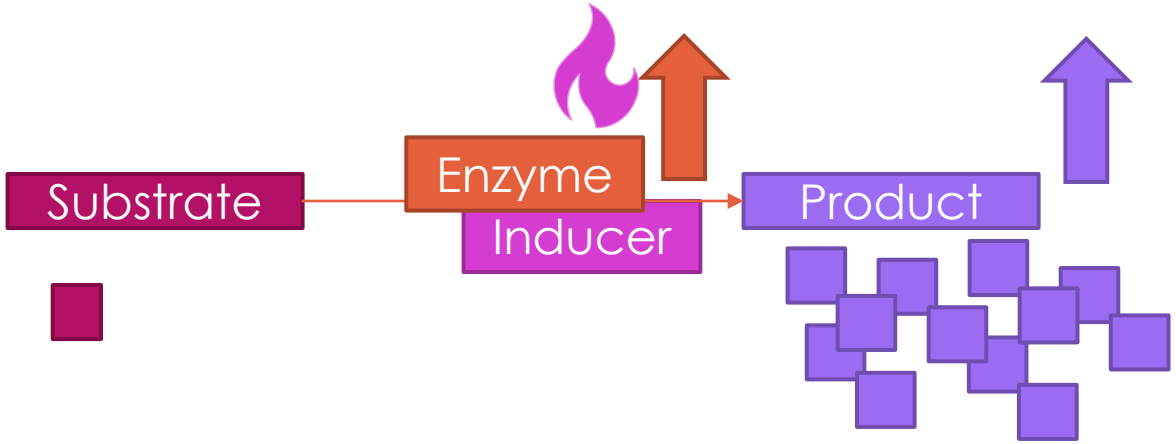


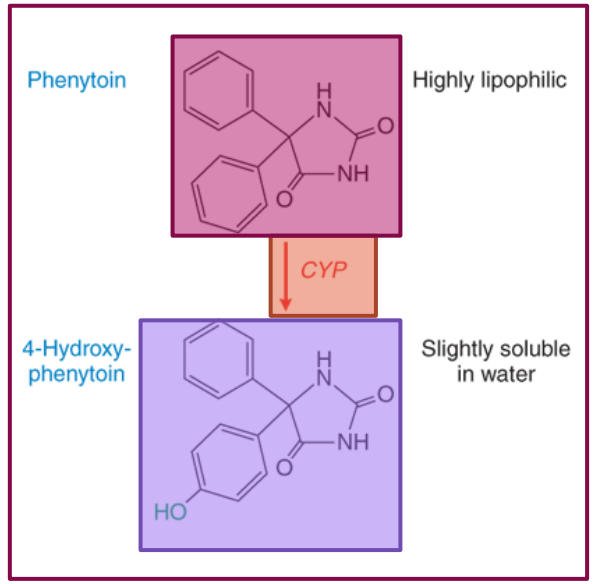
Inhibitor vs. Inducer

Normal Enzymatic Biotransformation



Biotransformation with Introduction of **Inducer**





FDA Definition – Inhibitor

Inhibitor Category	
Strong Inhibitor	Drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥5-fold
Moderate Inhibitor	Drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥2-fold to < 5-fold
Weak Inhibitor	Drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥1.25-fold to <2-fold
AUC: Area Under Curve	

For Healthcare Professionals | FDA's Examples of Drugs that Interact with CYP Enzymes and Transporter Systems https://www.fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems Accessed 15 JAN 2024

Strong CYP3A4 Inhibitors

- ceritinib
- clarithromycin
- cobicistat
- elvitegravir and ritonavir
- idelalisib
- indinavir and ritonavir
- lopinavir and ritonavir
- nefazodone
- nelfinavir
- paritaprevir and ritonavir
- ombitasvir and/or dasabuvir
- posaconazole
- ritonavir
- saquinavir and ritonavir
- telithromycin
- tipranavir and ritonavir
- voriconazole

For Healthcare Professionals | FDA's Examples of Drugs that Interact with CYP Enzymes and Transporter Systems https://www.fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems Accessed 15 JAN 2024

FDA Definition – Inducer

Inducer Category	
Strong Inducer	Drugs that decrease the AUC of sensitive substrates of a given metabolic pathway by ≥80%
Moderate Inducer	Drugs that decrease the AUC of sensitive substrates of a given metabolic pathway by ≥50% to <80%
Weak Inducer	Drugs that decrease the AUC of sensitive substrates of a given metabolic pathway by ≥20% to <50%
AUC: Area Under Curve	

For Healthcare Professionals | FDA's Examples of Drugs that Interact with CYP Enzymes and Transporter Systems https://www.fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems Accessed 15 JAN 2024

Strong CYP3A4 Inducers

- apalutamide
- carbamazepine
- enzalutamide
- ivosidenib
- lumacaftor and ivacaftor
- mitotane
- phenytoin
- rifampin
- St. john's wort

For Healthcare Professionals | FDA's Examples of Drugs that Interact with CYP Enzymes and Transporter Systems https://www.fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems Accessed 15 JAN 2024

Protocolspeak: Prohibited Medications

7.9.1. Concomitant Therapies and Procedures

Medications and procedures prohibited within specific time periods prior to the first dose study drug are described in the eligibility criteria (Section 5).

The following medications and procedures are prohibited during treatment:

- In vitro metabolism studies indicated that [redacted] is metabolized by CYP3A. As a precaution, strong inhibitors and strong inducers of CYP3A are prohibited. In vitro studies also indicated that [redacted] is mainly catalyzed by UGT1A9. Therefore, medicines that are UGT1A9 inhibitors and inducers are prohibited.
- For Parts 1A: Moderate and strong inhibitors and inducers of CYP3A are prohibited.
- For Parts 1D and 2D: Moderate and strong inhibitors of CYP3A are prohibited due to the potential for a drug-drug interaction with ribociclib.
- In vitro drug transporter studies have demonstrated that [redacted] is a dual substrate of P-gp and BCRP efflux transporters. Therefore, medicines that are P-gp and BCRP inhibitors are prohibited.
- In vitro studies demonstrated that [redacted] has the potential to inhibit CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5. Therefore, sensitive substrates of CYP1A2, 2C8, 2C9, 2C19, 2D6 and 3A4/5 with a narrow therapeutic index should be used with caution during the study.
- In vitro transporter studies have indicated that [redacted] is a moderate inhibitor of BCRP and OATP1B1. Therefore, substrates of these transporters with a narrow therapeutic index should be used with caution during the study.

How do I know which is which?

- Utilize Good References
  - Protocol
  - Lexicomp
  - Package Insert
  - Credible Meds
  - FDA Drug Interactions
- Interpret references in the clinical context of the patient
- Utilize resources appropriately
- Ask a pharmacist if you have questions!

Poll Question

Where are the majority of drugs metabolized?

a. Liver

b. Lungs

c. Kidney

d. Gallbladder

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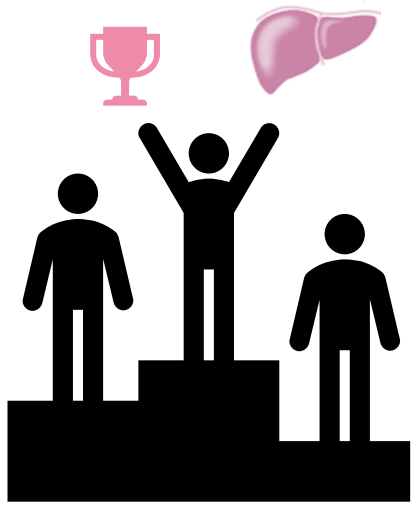


Poll Question

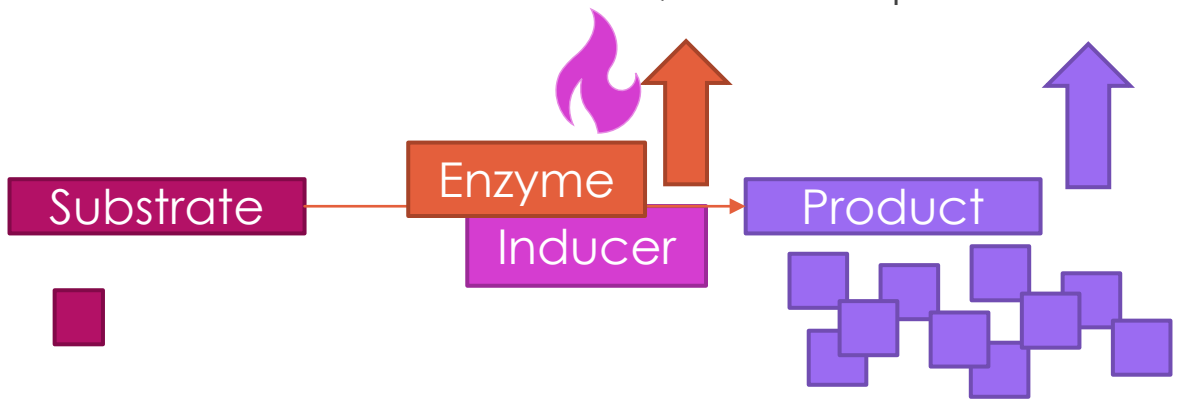
MADEUPINIB is metabolized by CYP3A4 to inactive metabolites and then excreted. Administering MADEUPINIB with carbamazepine (a CYP3A4 inducer) will have what effect on the efficacy of MADEUPINIB?

a. No effect

b. Increase rate of metabolism to inactive metabolite; decrease plasma concentration time in effective window

c. Increase rate of metabolism to inactive metabolite; increase plasma concentration time in effective window

d. Decrease rate of metabolism to inactive metabolite; decrease plasma concentration time in effective window



Poll Question

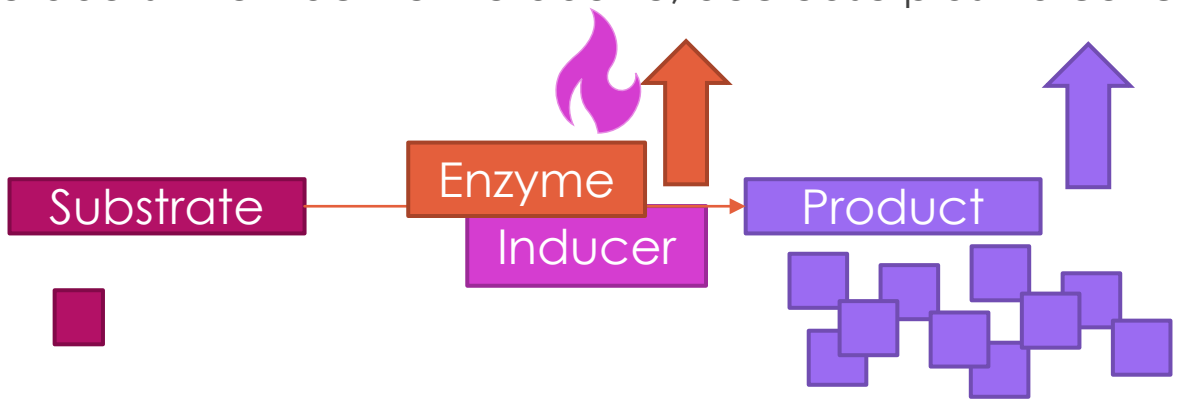
MADEUPINIB is metabolized by CYP3A4 to inactive metabolites and then excreted. Administering MADEUPINIB with carbamazepine (a CYP3A4 inducer) will have what effect on the efficacy of MADEUPINIB?

a. No effect

b. **Increase rate of metabolism to inactive metabolite; decrease plasma concentration time in effective window**

c. Increase rate of metabolism to inactive metabolite; increase plasma concentration time in effective window

d. Decrease rate of metabolism to inactive metabolite; decrease plasma concentration time in effective window



Poll Question

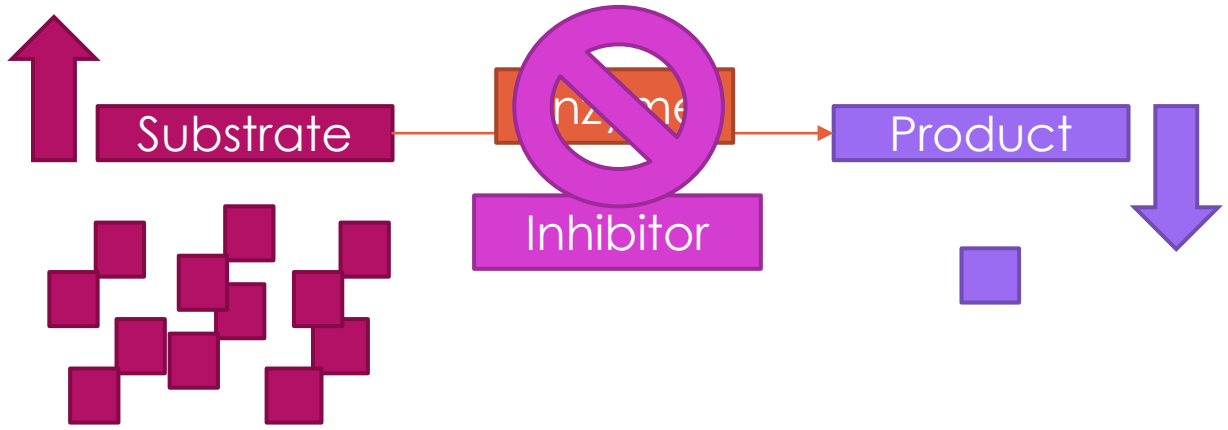
IMAGINMAB is metabolized by CYP1A2 to an inactive metabolite and then excreted. IMAGINMAB has a narrow therapeutic index and many off-target effects. Administering IMAGINMAB together with a course of ciprofloxacin (antibiotic; CYP1A2 strong inhibitor) would have which clinical effect?

a. No effect

b. Increase likelihood of adverse effects

c. Decrease likelihood of adverse effects

d. Eradicate infection faster



Poll Question

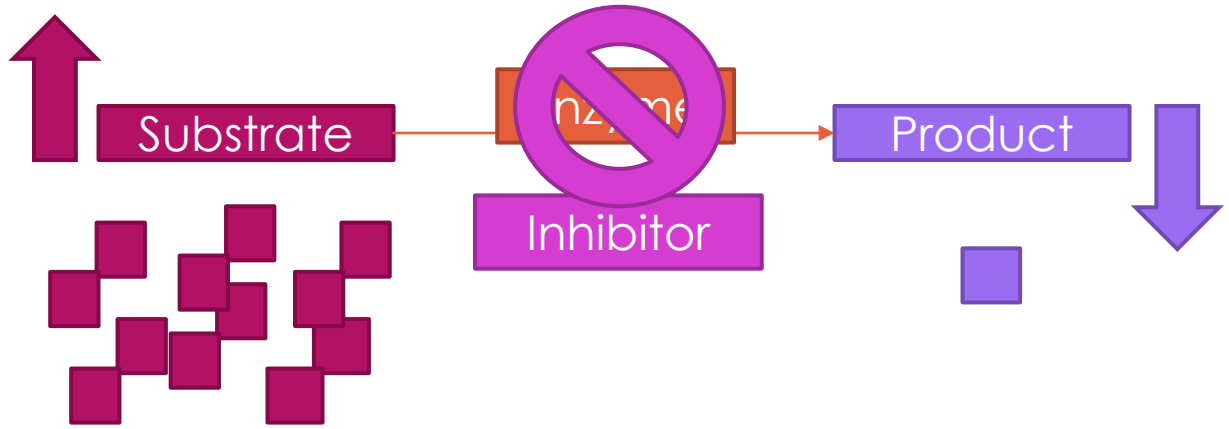
IMAGINMAB is metabolized by CYP1A2 to an inactive metabolite and then excreted. IMAGINMAB has a narrow therapeutic index and many off-target effects. Administering IMAGINMAB together with a course of ciprofloxacin (antibiotic; CYP1A2 strong inhibitor) would have which clinical effect?

a. No effect

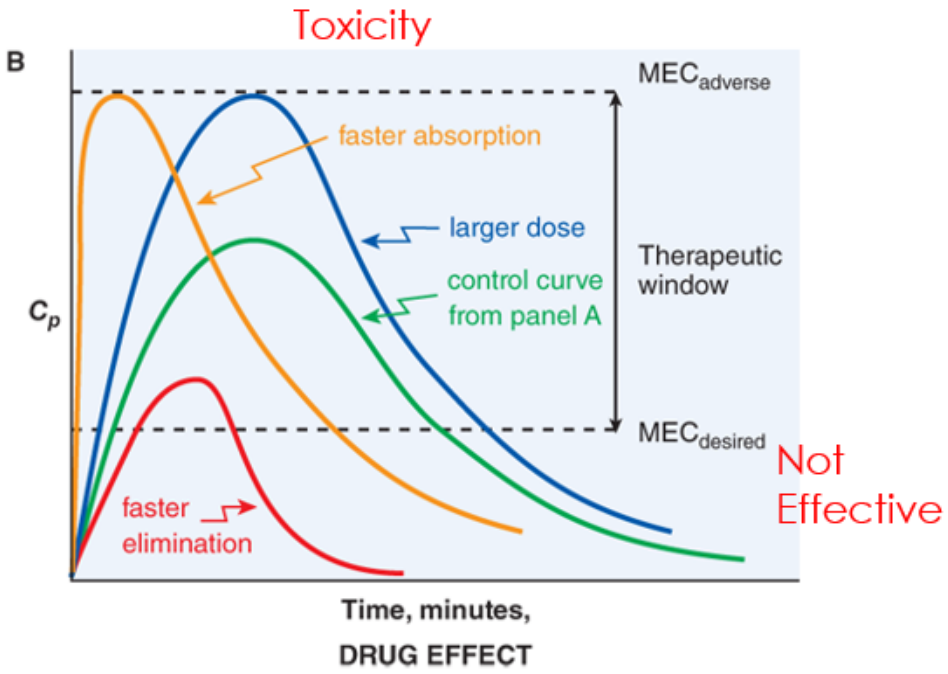
b. **Increase likelihood of adverse effects**

c. Decrease likelihood of adverse effects

d. Eradicate infection faster



End of Part I: Questions?



Activity Code (Part 1)

Activity Code: **150957**

Instructions for claiming credits/contact hours can be found here.