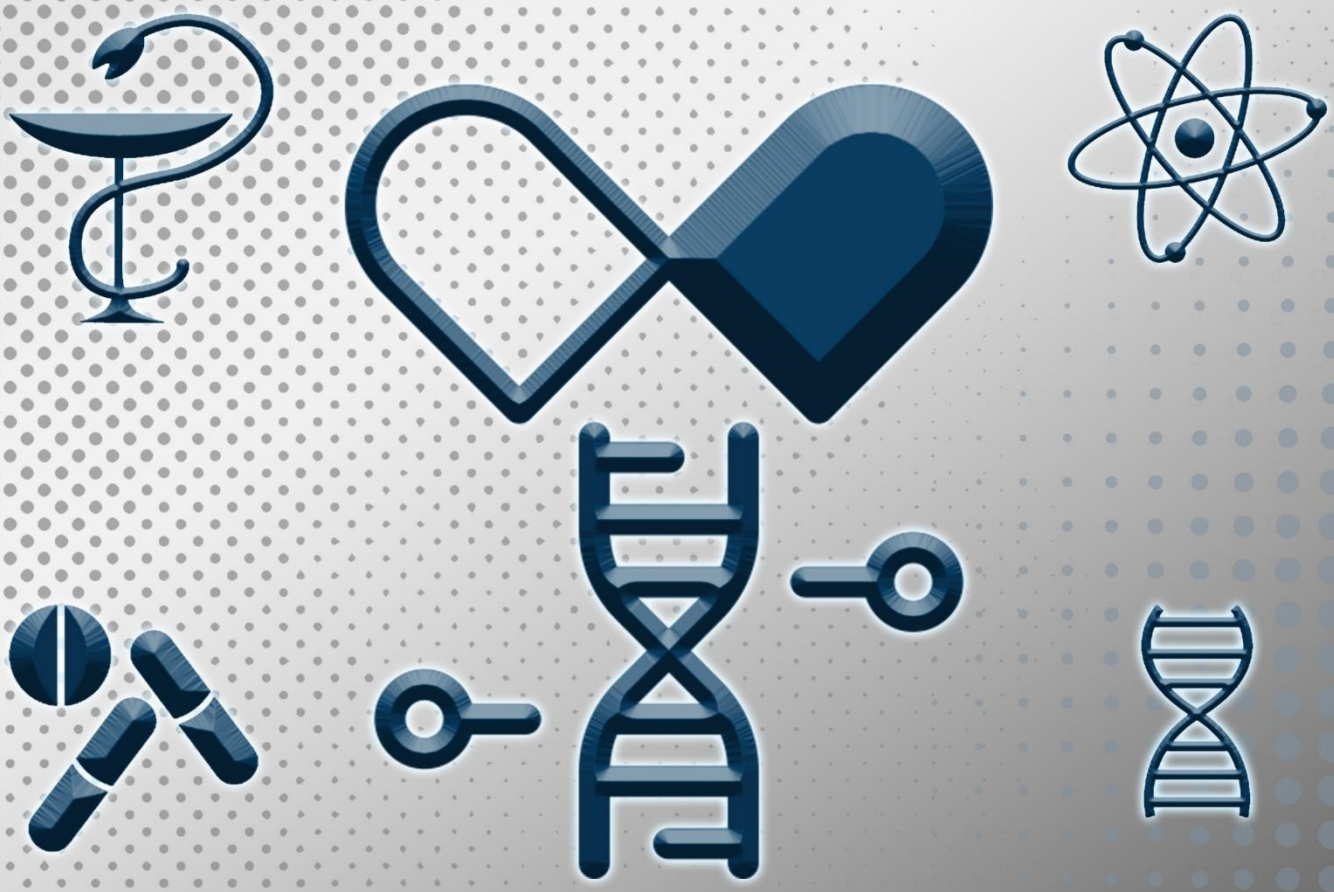
Pharmacology



Done By:

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Drug Biotransformation (Metabolism):

Introduction

- Tissues that act as portals for entry of external molecules into our body contain transporters that expel unwanted molecules immediately after absorption (**i.e., MDR family [P-glycoproteins]**).
  - However, many foreign molecules evade these gatekeepers and are absorbed.
  - Thus, to eliminate them we need a mechanism for excreting those undesirable substances.
    - ➔ Biotransformation of drugs is one such process.
- Where does drug Biotransformation occur?
  - Every tissue has some ability to metabolize drugs:
    - ➔ Liver is the principal organ of drug metabolism.
    - ➔ Gastrointestinal tract, lungs, skin, kidneys, brain.
- What determines drug Biotransformation Rate?
  - Vary markedly among different individuals, due to:
    - ➔ Genetic Factors
      - Polymorphisms of drug enzyme genes in different ppl.
    - ➔ Effects of Other Drugs
      - Coadministration of certain agents may alter the disposition of many drugs.
      - Mechanisms include the following:
        - ⇨ Enzyme induction
          - Increased rate and extent of metabolism
          - Induction usually results from increased synthesis of cytochrome P450 drug-oxidizing enzymes & heme cofactor.
          - The most common strong inducers: carbamazepine, phenobarbital, phenytoin, and rifampin.
        - ⇨ Enzyme inhibition
          - Decreased rate and extent of metabolism
          - Most important ones: amiodarone, cimetidine, furanocoumarins present in grapefruit juice, azole antifungals, and the HIV protease inhibitor ritonavir.
          - Suicide inhibitors:
            - The drugs that are metabolized to products that irreversibly inhibit CYP450.
            - Such agents include ethinyl estradiol, norethindrone, spironolactone, secobarbital, allopurinol, fluroxene, and propylthiouracil.
        - ⇨ Inhibitors of intestinal P-glycoprotein
          - P-glycoprotein (P-gp):
            - Important modulator of intestinal drug transport
            - Also found in BBB and in drug-resistant cancer cells.
            - Functions to expel drugs from intestinal mucosa into the lumen,
            - Thus, contributing to first pass elimination.
          - Drugs that inhibit intestinal P-gp mimic drug metabolism inhibitors:
            - By increasing bioavailability (↑Plasma concentration of the drug).
          - P-gp inhibitors include verapamil, mibefradil and furanocoumarin (grapefruit juice).
          - Drugs expelled by P-gp include digoxin, cyclosporine, and saquinavir.
            - Therefore, it is potentially more toxic when given with a P-gp inhibitor.
    - ➔ Age, Gender & Diseases

TYPES OF METABOLIC REACTIONS

- Phase I Reactions:
  - Include oxidation (esp. by the CYP450), reduction, deamination, and hydrolysis.
  - CYP450 enzymes are found in high concentrations in smooth endoplasmic reticulum of the liver.
    - ➔ They are not highly selective in their substrates,
    - ➔ Small numbers can metabolize thousands of drugs.
  - Of the drugs metabolized by phase I cytochrome P450s:
    - ➔ 75% are metabolized by just two: CYP3A4/5 or CYP2D6.
    - ➔ CYP3A4 & 3A5 are responsible for metabolism of 50% of drugs.
  - Convert the parent drug to a more polar metabolite.
    - ➔ Often these metabolites are inactive or may be enhanced.
    - ➔ Prodrugs: drugs taken as inactive but activated after absorption.

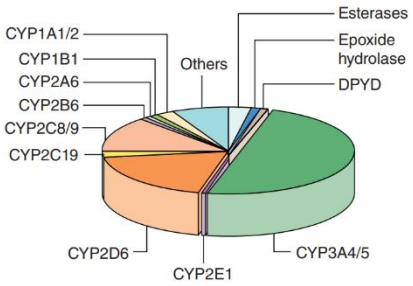


TABLE 4–1 Examples of phase I drug-metabolizing reactions.

Reaction Type	Typical Drug Substrates
Oxidations, P450 dependent	
Hydroxylation	Amphetamines, barbiturates, phenytoin, warfarin
N-dealkylation	Caffeine, morphine, theophylline
O-dealkylation	Codeine
N-oxidation	Acetaminophen, nicotine
S-oxidation	Chlorpromazine, cimetidine, thioridazine
Deamination	Amphetamine, diazepam
Oxidations, P450 independent	
Amine oxidation	Epinephrine
Dehydrogenation	Chloral hydrate, ethanol
Reductions	Chloramphenicol, clonazepam, dantrolene, naloxone
Hydrolyses	
Esters	Aspirin, clofibrate, procaine, succinylcholine
Amides	Indomethacin, lidocaine, procainamide

- Phase II Reactions
  - Synthetic reactions that involve addition (conjugation) of subgroups to functions on the drug.
  - The subgroups that are added include:
    - ➔ Glucuronate, acetate, glutathione, glycine, sulfate, —OH, —NH2, —SH and methyl groups.
    - ➔ Enzymes are not very selective.

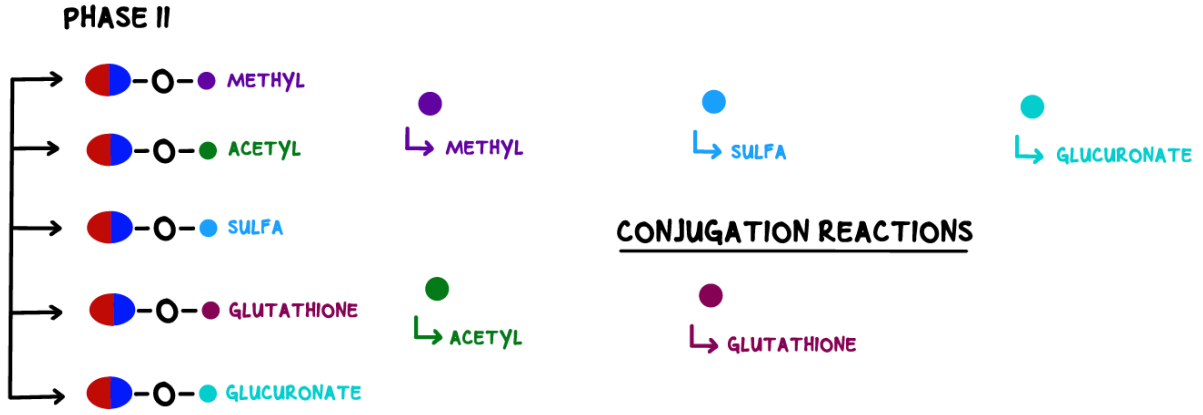
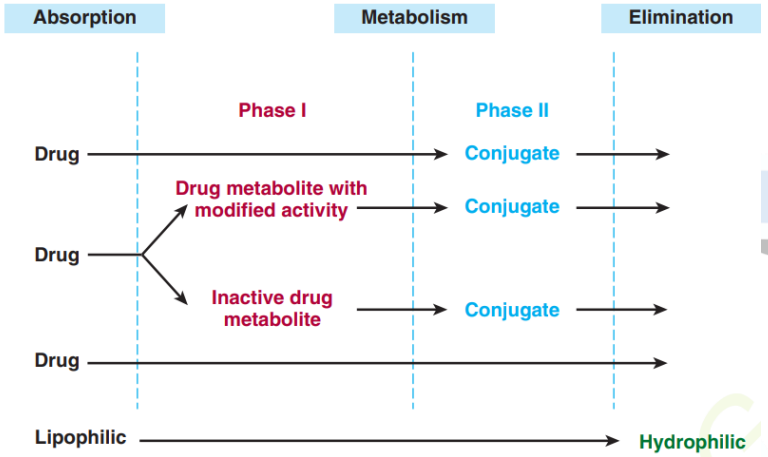


TABLE 4–2 Examples of phase II drug-metabolizing reactions.

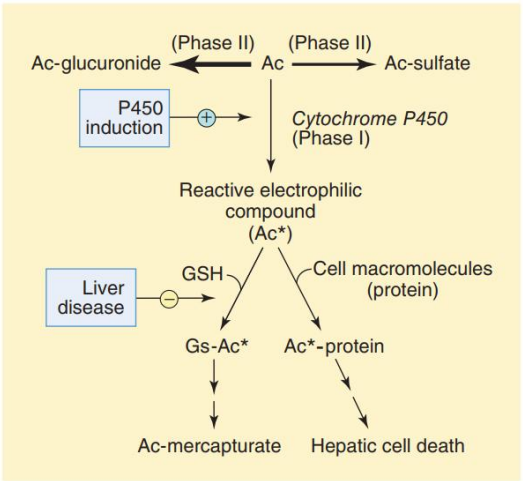
Reaction Type	Typical Drug Substrates
Glucuronidation	Acetaminophen, diazepam, digoxin, morphine, sulfamethiazole
Acetylation	Clonazepam, dapsone, isoniazid, mescaline, sulfonamides
Glutathione conjugation	Ethacrynic acid, reactive phase I metabolite of acetaminophen
Glycine conjugation	Deoxycholic acid, nicotinic acid (niacin), salicylic acid
Sulfation	Acetaminophen, methyldopa
Methylation	Dopamine, epinephrine, histamine, norepinephrine, thiouracil

- Drugs that are metabolized by both routes may undergo phase II before or after phase I.
  - Mainly phase II reactions may precede phase I reactions.



TOXIC METABOLISM:

- Drug metabolism is not synonymous with drug inactivation.
- Some drugs are converted to active products by metabolism.
- If these products are toxic, severe liver injury maybe resulted.
  - An important example is acetaminophen (paracetamol) in large overdoses.
  - Acetaminophen metabolism:
    - ➔ Phase II:
      - In recommended doses by patients with normal liver function.
      - Conjugated to harmless glucuronide and sulfate metabolites.
      - In large overdoses, the phase II metabolic pathways are overwhelmed & phase I work.
    - ➔ Phase I:
      - P450-dependent system converts some of drug to (N-acetyl-p-benzoquinoneimine)
      - If glutathione stores are adequate.
        - ⇨ NAPQI is conjugated with glutathione to a third harmless product.
      - If no glutathione is present:
        - ⇨ NAPQI combines with sulfhydryl groups on hepatic cell proteins, resulting in cell death.



- In severe liver disease, stores of glucuronide, sulfate, and glutathione may be depleted, making the patient more susceptible to hepatic toxicity with near-normal doses of acetaminophen.
- Antidote of paracetamol toxicity: administration **acetylcysteine** may be lifesaving.
    - **Acetylcysteine** is a sulfhydryl donor.

- Enzyme inducers (eg, ethanol) may increase acetaminophen toxicity because they increase phase I metabolism more than phase II metabolism, thus resulting in increased production of the reactive metabolite.

QUESTIONS

Questions 1–2. You are planning to treat chronic major depression in a 35-year-old patient with recurrent suicidal thoughts. She has several comorbid conditions that require drug therapy. You are concerned about drug interactions caused by changes in drug metabolism in this patient.

1. Drug metabolism in humans usually results in a product that is
   (A) Less lipid soluble than the original drug
   (B) More likely to distribute intracellularly
   (C) More likely to be reabsorbed by kidney tubules
   (D) More lipid soluble than the original drug
   (E) Less water soluble than the original drug

2. If therapy with multiple drugs causes induction of drug metabolism in your depressed patient, it will
   (A) Be associated with increased smooth endoplasmic reticulum
   (B) Be associated with increased rough endoplasmic reticulum
   (C) Be associated with decreased enzymes in the soluble cytoplasmic fraction
   (D) Require 3–4 months to reach completion
   (E) Be irreversible

3. Which of the following factors is likely to increase the duration of action of a drug that is metabolized by CYP3A4 in the liver?
   (A) Chronic administration of rifampin during therapy with the drug in question
   (B) Chronic therapy with amiodarone
   (C) Displacement from tissue-binding sites by another drug
   (D) Increased cardiac output
   (E) Chronic administration of carbamazepine

4. Reports of cardiac arrhythmias caused by unusually high blood levels of 2 antihistamines, terfenadine and astemizole, led to their removal from the market. Which of the following best explains these effects?
   (A) Concomitant treatment with rifampin
   (B) Use of these drugs by chronic alcoholics
   (C) Use of these drugs by chronic smokers

(D) Treatment of these patients with ketoconazole, an azole antifungal agent

5. Which of the following agents, when used in combination with other anti-HIV drugs, permits dose reductions?
   (A) Cimetidine
   (B) Efavirenz
   (C) Ketoconazole
   (D) Procainamide
   (E) Quinidine
   (F) Ritonavir
   (G) Succinylcholine
   (H) Verapamil

6. Which of the following drugs may inhibit the hepatic microsomal P450 responsible for warfarin metabolism?
   (A) Amiodarone
   (B) Ethanol
   (C) Phenobarbital
   (D) Procainamide
   (E) Rifampin

7. Which of the following drugs, if used chronically, is most likely to increase the toxicity of acetaminophen?
   (A) Cimetidine
   (B) Ethanol
   (C) Ketoconazole
   (D) Procainamide
   (E) Quinidine
   (F) Ritonavir
   (G) Succinylcholine
   (H) Verapamil

8. Which of the following drugs has higher first-pass metabolism in men than in women?
   (A) Cimetidine
   (B) Ethanol
   (C) Ketoconazole
   (D) Procainamide
   (E) Quinidine
   (F) Ritonavir
   (G) Succinylcholine
   (H) Verapamil

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9. Which of the following drugs is an established inhibitor of P-glycoprotein (P-gp) drug transporters?
   (A) Cimetidine
   (B) Ethanol
   (C) Ketoconazole
   (D) Procainamide
   (E) Quinidine
   (F) Ritonavir
   (G) Succinylcholine
   (H) Verapamil

10. Which of the following cytochrome isoforms is responsible for metabolizing the largest number of drugs?
   (A) CYP1A2
   (B) CYP2C9
   (C) CYP2C19
   (D) CYP2D6
   (E) CYP3A4

THE END OF CHAPTER 4

حبُّ السلامةِ يُثني همَّ صاحبِه
عن المعالي ويُغري المرءَ بالكَسلِ