# PHARMACOKINETICS – II
# Metabolism & Excretion

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## OUTLINE

A. DRUG METABOLISM
   I. Phase I and II reactions
   II. CYP- 450 enzyme system
   III. First- pass metabolism

B. EXCRETION OF DRUGS
   I. Renal excretion
   II. Biliary excretion

## DRUG ELIMINATION

- ....is the irreversible loss of drug from the body. It occurs by two processes: metabolism and excretion
- Humans have evolved complex systems that detoxify foreign chemicals (xenobiotics), including carcinogens and toxins present in their diet
- The ability of humans to metabolize and clear drugs is a natural process that involves the same enzymatic pathways and transport systems that are used for normal metabolism of dietary constituents

## DRUG METABOLISM

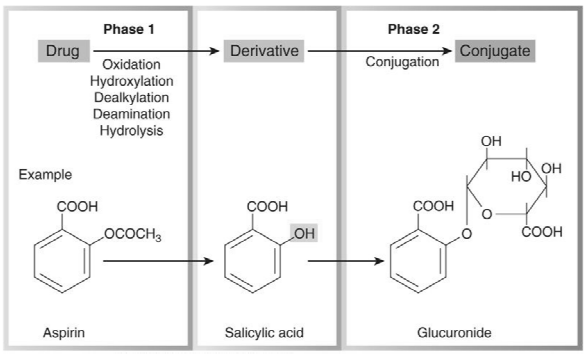
- The lipophilic nature of drugs promote passage through biological membranes and thereby,
  a. allow subsequent access to their sites of action giving therapeutic effects
  b. hinder their excretion from the body
- ∴ metabolism of drugs into more hydrophilic metabolites is essential for their elimination from the body, as well as for termination of their biological and pharmacological activity

## DRUG METABOLISM

- In general, biotransformation reactions generate more polar, inactive metabolites that are readily excreted from the body
- Exceptions include prodrugs that are converted into more active substances after metabolism
  e.g. enalapril

## DRUG METABOLISM

- Classified into two types:
  1. **Phase I (functionalization) reactions**
     .....introduce or expose a functional group on the parent compound
  2. **Phase II (biosynthetic / conjugation) reactions**
     **...** involve conjugation of a reactive group (often inserted during phase I reaction)

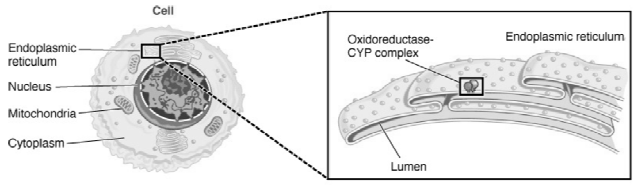



## DRUG METABOLISM

- Phase I reactions - result in the biological inactivation of the drug
- Phase II reactions - produce a metabolite with improved water solubility, facilitating the excretion of the drug from the body

## SITE OF DRUG METABOLISM

- Metabolizing enzymes are located in
  1. **Liver**
  2. Small and large intestines
  3. Lungs
- Phase I enzyme systems - in the endoplasmic reticulum
- Phase II enzyme systems - mainly cytosolic




## PHASE 1 REACTIONS

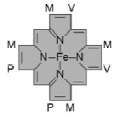
- Phase I enzymes either adds or exposes a functional group, permitting the products of phase I metabolism to serve as substrates for the phase II conjugating or synthetic enzymes
- Phase I reactions involve oxidation, reduction and hydrolysis.

## PHASE 1 REACTIONS

- Phase I oxidation reactions are carried out by,
  1. **Cytochrome P-450 Superfamily (CYPs)**
  2. Flavin-containing monooxygenases
  3. Epoxide hydrolases

## THE CYTOCHROME P-450 SUPERFAMILY

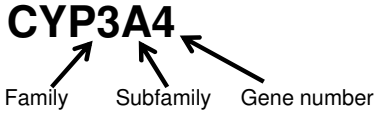
- The CYPs are a superfamily of enzymes, all of which contain a molecule of haeme that is non-covalently bound to the polypeptide chain




- More than 50 individual CYPs have been identified in humans.

## THE CYTOCHROME P-450 SUPERFAMILY

- Based on amino acid sequence similarities in the genes grouped into a superfamily composed of families and subfamilies




## THE CYTOCHROME P-450 SUPERFAMILY

- In humans, three main CYP families (**CYP1, CYP2** and **CYP3**) are involved in drug metabolism
- CYP3A4 is involved in the metabolism of over 50% of clinically used drugs
- CYPs - mainly located in liver
  - throughout the GI tract
  - in lower amounts in lung, kidney and CNS

## THE CYTOCHROME P-450 SUPERFAMILY

- CYPs have the capacity to metabolize diverse chemicals due to
  a. multiple forms of CYPs
  b. the capacity of a single CYP to metabolize many structurally distinct chemicals
  c. a single compound can also be metabolized by different CYPs
- This property is due to large and fluid substrate binding sites in the CYP

## THE CYTOCHROME P-450 SUPERFAMILY

- Overlapping substrate specificity of CYPs lead to....
  i. Slower metabolic rate
  ii. drug-drug interactions

## CYPS AND DRUG-DRUG INTERACTIONS

- Drug- drug interactions commonly inhibit the drug metabolism by CYPs but sometimes induces the enzyme action
- The most common mechanism of enzyme induction is transcriptional activation leading to increased synthesis of more CYP enzyme proteins

## CYPS AND DRUG-DRUG INTERACTIONS

- Mechanisms of CYP inhibition:
  a. When two drugs metabolised by the same CYP enzyme – competitive inhibition
     e.g. Simvastatin and Erythromycin
  b. Some drugs compete for the active site but are not themselves substrates – competitive inhibition
     e.g. Quinidine inhibitor of CYP2D6
  c. Independently of being substrates for a CYP – non-competitive inhibition
     e.g. Ketoconazole- by forming a tight complex with the haem moiety of CYP3A4

## CYPS AND DRUG-DRUG INTERACTIONS

- Drug- drug interactions commonly occur when two drugs are co-administered and subjected to metabolism by the same enzyme
- Thus, it is important to determine the identity of the CYP that metabolizes a particular drug and to avoid co-administering drugs that are metabolized by the same enzyme

## CLINICALLY IMPORTANT CYP INHIBITORS & INDUCERS

| CYP INHIBITORS | CYP INDUCERS |
|---|---|
| CIMETIDINE | BARBITURATES |
| SOME MACROLIDES | CARBAMAZEPINE |
| SOME ANIFUNGALS | PHENYTOIN |
| SOME 4-QUINOLONES | RIFAMPICIN |
| SOME HIV AGENTS | ETHANOL (CYP2E1) |
| GRAPEFRUIT JUICE | CIGARETTE SMOKE |

Case report

Psychopharm

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### Recurrent relapses of depression in a patient established on sertraline after taking herbal medicinal mixtures – a herb–drug interaction?

**Abstract**

We describe a patient with depression who was well controlled with sertraline monotherapy developing two relapses of depression in close temporal relationship with starting ayurvedic herbal mixtures. We discuss the possibility of a pharmacokinetic herb–drug interaction decreasing the therapeutic efficacy of sertraline leading to the relapses of depression. We speculate the herbal plant most likely to be responsible for this interaction is either *Terminalia chebula* or *Commiphora wightii*.

## Flavin-Containing Monooxygenases (FMOs)

- Another superfamily of phase I enzymes involved in drug metabolism
- Similar to CYPs, the FMOs are expressed at high levels in the liver and are bound to the endoplasmic reticulum
- Minor contributors to drug metabolism
- In contrast to CYPs,FMOs are not induced or easily inhibited ⇒ not involved in drug-drug interactions

## PHASE II REACTIONS

- Involve conjugation of a reactive group and usually lead to inactive and polar products that are readily excreted
- However morphine and minoxidil, glucuronide and sulfate conjugates, respectively, are more pharmacologically active than the parent

## PHASE II REACTIONS

- Include several superfamilies of conjugating enzymes.
  - e.g. Glutathione-S-transferases
  - UDP-glucuronosyltransferases
  - Sulfotransferases
  - N-acetyltransferases
  - Methyltransferases

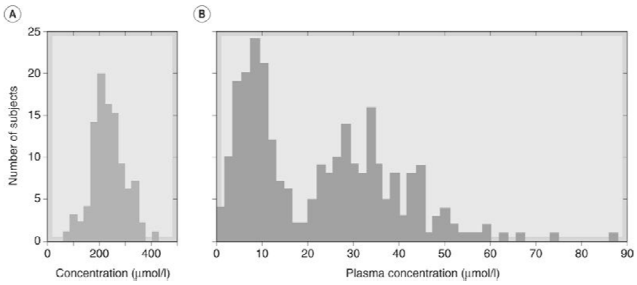
## PHASE II REACTIONS

- The catalytic rates of phase 2 reactions are significantly faster than the rates of the CYPs

The rate limiting step of drug metabolism is the initial (phase I) oxidation reaction

## N-ACETYLATION

- Following the discovery of isoniazid 5-15% of patients on isoniazid experienced toxicities that ranged from numbness and tingling in their fingers to CNS damage
- Elimination of isoniazid depends mainly on acetylation, catalysed by an acetyltransferase enzyme




**Distribution of individual plasma concentrations for two drugs in humans. [A] Aspirin [B] Isoniazid**

## N-ACETYLATION

- Pharmacogenetic studies led to the classification of "rapid" and "slow" acetylators, with the "slow" phenotype being predisposed to toxicity

## FIRST-PASS METABOLISM

- Metabolic inactivation of a significant proportion of an orally administered drug before the drug reaches the systemic circulation
- This occurs either the intestinal epithelium or the liver

## FIRST-PASS METABOLISM

- First-pass metabolism significantly limits the oral bioavailability of highly metabolized drugs
- As a result a much larger dose of the drug is needed when it is given orally than when it is given parenterally

## FIRST-PASS METABOLISM

| DRUGS THAT UNDERGO SUBSTANTIAL FIRST-PASS METABOLISM |
|---|
| Aspirin |
| Metoprolol |
| Glyceryl trinitrate |
| Morphine |
| Propranolol |
| Levodopa |
| Salbutamol |
| Verapamil |

## EXCRETION OF DRUGS

- Excretory organs except lungs eliminate polar compounds more efficiently than substances with high lipid solubility
- Routes of excretion
  - Renal
  - Gastrointestinal
  - Lungs
  - Breast milk

## RENAL EXCRETION

- Involves three distinct processes:
  1. Glomerular filtration
  2. Active tubular secretion
  3. Passive tubular reabsorption

## GLOMERULAR FILTRATION

- The amount of drug entering the tubular lumen by filtration depends on..
  1. Glomerular filtration rate
  2. Extent of plasma binding of the drug
- Up to 20% of renal plasma flow is filtered through the glomerulus

## TUBULAR SECRETION

- ~ 80% of the drug delivered to the kidney is presented to the PCT via peritubular capillaries

Tubular secretion is potentially the most effective mechanism of renal drug elimination

- Occurs via carrier-mediated membrane transporters against a concentration gradiant

## TUBULAR SECRETION

- Unlike glomerular filtration, carrier-mediated transport can achieve maximal drug clearance even when most of the drug is bound to plasma proteins
  e.g. Penicillin
  (although ~ 80% protein bound and therefore cleared only slowly by filtration, almost completely removed by proximal tubular secretion)

## TUBULAR SECRETION

- Many drugs compete for the same transport system ⇒ drug interactions
  e.g. Probenecid - prolong the action of penicillin by retarding its tubular secretion

## TUBULAR REABSORPTION

- ~99% water in the glomerular filtrate is reabsorbed as fluid traverses the tubule
- Create a concentration gradient for drug molecules
- If lipid soluable the drug will be reabsorbed passively down concentration gradient

## TUBULAR REABSORPTION

- Lipid-soluble drugs are therefore excreted poorly, whereas polar drugs of low tubular permeability remain in the lumen and become progressively concentrated as water is reabsorbed
  e.g. digoxin and *aminoglycoside antibiotics*
- The degree of ionization of many drugs-weak acids or weak bases-is pH dependent, and this markedly influences their renal excretion

## RENAL EXCRETION

- For drugs not inactivated by metabolism, the rate of renal elimination is the main factor that determines their duration of action
  e.g. Frusemide, gentamicin, digoxin, methotrexate
- These drugs have to be used with special care in individuals whose renal function may be impaired, including the elderly and patients with renal disease

## RENAL CLEARANCE

- Elimination of drugs by the kidneys is best quantified by the renal clearance ($CL_r$)
- Defined as the volume of plasma containing the amount of substance that is removed from the body by the kidneys in unit time

## RENAL CLEARANCE

$$CL_r = \frac{C_u \times V_u}{C_p}$$

$C_p$ - plasma concentration
$C_u$ - urinary concentration
$V_u$ - rate of flow of urine

## BILIARY EXCRETION

- Transporters present in the canalicular membrane of the hepatocyte actively secrete drugs and metabolites into bile
  e.g. Vecuronium , Rifampicin
- Drugs and metabolites present in bile are released into the GI tract during the digestive process

## ENTEROHEPATIC RECYCLING

- Drugs and metabolites being reabsorbed back into the body from the intestine (in the case of conjugated metabolites, require their enzymatic hydrolysis by the intestinal microflora)
- Create a 'reservoir' of recirculating drug that can amount to about 20% of total drug in the body and prolongs drug action
  e.g. Morphine, ethinylestradiol

## SUMMARY

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## Thank you !