Pharmacokinetics III: Metabolism & Excretion

PHC 721

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Metabolism

(a.k.a. Biotransformation)

1) Formation of pharmacologically active drug metabolites (Phase I)
(observed effect = drug effect + drug metabolite effect; e.g., Morphine, Codeine, Diazepam)
2) Conversion of inactive drugs (Prodrugs) to pharmacologically active metabolites
(e.g., Acyclovir, Bacampicillin, Clopidogrel, Levodopa, Methyldopa)
3) Inactivation of drugs and metabolites ('detoxification'; Phase I & Phase II)
(e.g., Acetaminophen, Ibuprofen, Lidocaine, Propranolol)
4) Conversion: Nonpolar → Polar (lipid-insoluble) for renal/biliary excretion (Phase II)
(lipid insolubility prevents reabsorption in renal tubules and bile ducts)
The primary site for drug metabolism is LIVER; others: KIDNEY, INTESTINE, LUNGS, PLASMA
***Most water-soluble drugs are not biotransformed* and are excreted unchanged**
(e.g., Gentamicin, Neostigmine)

Phase I Reactions
Non-Synthetic (active/inactive metabolites)**:**
Oxidation, Reduction, Hydrolysis
Hemoprotein Cytochrome P450 (CYP) isoenzyme families (e.g., CYP3A4, CYP2D6).
1) Microsomal ⇒ inducible by drugs/food
2) Non-Microsomal ⇒ not inducible; genetic polymorphisms

Phase II Reactions
Synthetic (mostly inactivating)**:**
Conjugation with Endogenous Groups
1) Microsomal (Hepatic & Non-Hepatic):
Glucuronide
2) Non-Microsomal (e.g., cytosol, nucleus):
Sulfate, Acetate, Glycine, etc. (except Glucuronide)
Glutathione:
prevents metabolism-induced drug toxicity
(e.g., quinone/epoxide from Acetaminophen)

Metabolism is sometimes called biotransformation. Those are fully interchangeable terms. First, what I wanted you to really pay attention to is the 4 different types of processes that comprise metabolism

Because we usually associate metabolism with drug inactivation for elimination from the body, metabolism is more complex than that. It's really critical for you to understand this because we will be coming back to this for the rest of our course. It's really important for your profession to understand well is that metabolism can lead to formation of pharmacologically active metabolites. In addition to the original drug being active, there's also metabolites that can be active. This applies to morphine, codeine, benzodiazepine, and diazepam. Morphine is converted to a more active metabolite than the morphine itself. Codeine is actually converted to morphine so also more active metabolite.

Another type is when the original drug is actually not active. it's called prodrug, and actually needs the biotransformation in order to become active. I wanted to point out clopidogrel because they are antiplatelet agent (we'll talk about hemostasis pretty soon). Again, inactive drugs or prodrug are drugs that have not acted by themselves, active metabolite is actually responsible for the action of the drug

The third type, in general we think metabolism is inactivation of drugs and metabolites. When you have formation of first active metabolite those active metabolites also need to be inactivated for elimination from the body. This process sometimes is called detoxification because all drugs are toxins. Inactivation meaning making them less harmful or not harmful at all to the body.

Final one is simply conversion from nonpolar to polar. Polar ionized forms are lipid in-cellular-able. If our lipid insoluble, they cannot pass through membranes. As we discussed both absorption and distribution without that, excretion just conversion to those left insoluble because when it slipped in-cellular-able, it cannot be reabsorbed.

Those are the 4 processes that comprise metabolism. The primary site is LIVER, but I want you to remember the other sides also responsible for metabolism. One more comment is that when we're dealing with a drug that is water soluble, those are not biotransformed for simple reason that they cannot get to the cells that are responsible for metabolism, such as the hepatocytes in gentamicin, neostigmine.

In general, the drug can be biotransformed when it's liquid soluble (non-ionized). This is an overview of metabolism processes.

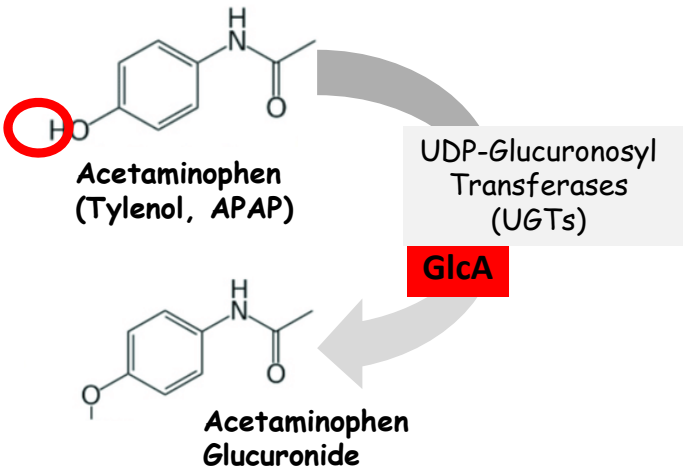
A few words about the phase one and phase two reactions.
Phase one reactions: those are called non-synthetic. Both active and inactive metabolites are made in this process. Both formation of active metabolites or inactive meaning inactivation of the drugs. Those would be the results of the non-synthetic rections services, step one reactions. You have here oxidation reduction hydrolysis and so on. By far, the most important type of enzyme and reaction that we will talk about will be that actions needed advice add from P450. Here are different isoenzymes different subtypes. We will discuss some of them in greater detail and for some drugs such as morphine, codeine. You wanted to remember which subtype actually it is because of the possibility move genetic differences in patients and then differences in metabolism. For now, just remember that phase one reactions, the most important ones, the most commonly used by the body, are the reactions mediated by the cytochrome P450 enzymes.
One more comment that's maybe less important for you clinically, but you may end up getting questions like this on the board exam. There are two locations for those enzymes: microsomes & non-microsomal. The difference is that the inducible by drugs/foods. We talk about the induction of enzymes when you increase the enzyme activity and by other drugs. For example, one of the major types of drug interactions is enzyme induction. Then, this would speed up the metabolism of the drug. So, inducible by drugs are located in microsomes. Those that are not microsomes are non inducible. Those non-microsomes undergo that genetic programs, meaning are affected by genetic polymorphisms. As I mentioned earlier (about P450), different patients would be the ones located by in non-microsomal site. This is phase one reactions.

Phase two reactions are synthetic. Unlike the phase one nonsynthetic, here we have synthetic. The synthesis will be conjugation with endogenous groups. Cell conjugation will lead mostly to inactivation. There are many different groups that the drugs can be conjugated with, but by far the most important is on conjugation with glucoronide. I will come back to the next slid. Glucoronide conjugation happens in microsomes. The non-microsomal site is where their actions happen of conjugation with other groups. The most important there is glutathione.

This slide is just an overview.

Metabolism

The most important Phase II (Synthetic) Reaction: Glucuronide Conjugation

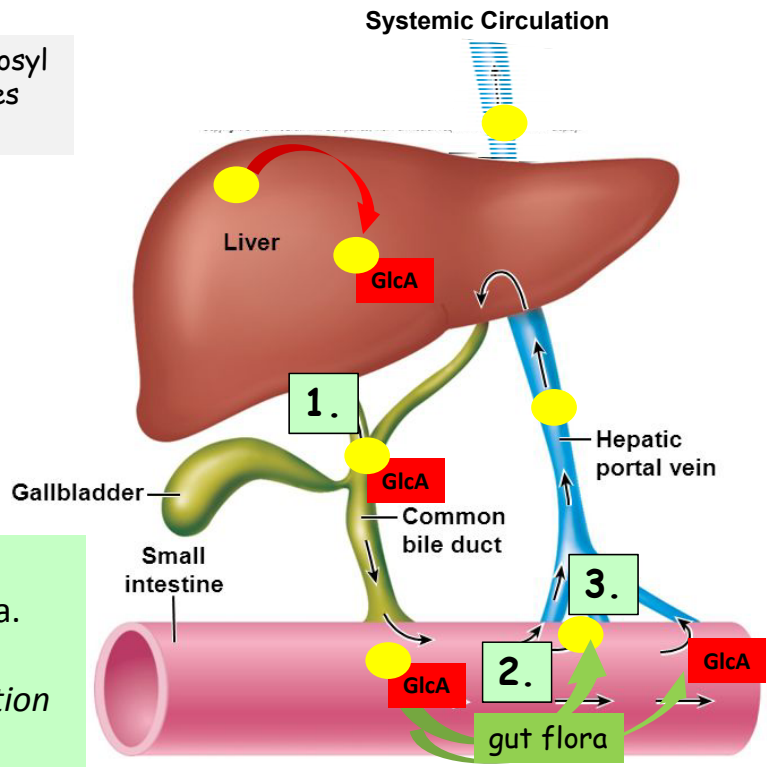


Other examples: Aspirin, Diazepam, Metronidazole, Morphine

1. Glucuronidation favors excretion in bile.
2. Hydrolysis of drug glucuronides by gut flora.
3. The released free drug is reabsorbed.

This enterohepatic cycling prolongs drug action (e.g., oral contraceptives).

Enterohepatic Cycling of Drugs



Phase II (Synthetic Reation):
Glucoronide Conjugation (the most important one): One of the most important drugs for you to know is Tylenol or acetaminophen (generic name). Here is the drug. Here's UDP glucuronic transferase. This is the whole family of them. They carry their gluconic acid (= glucuronide) and it replaces the hydrogen, so
we get acetaminophen gluconate.
Here are a few additional examples of drugs that are important for your profession.

I wanted to tell you about now is the phenomenon of **internal hepatic cycling of drugs**. Once the drug is conjugated with GlcA, It's likely to be excreted in bile, so it ends up in the bile duct. From there, it gets to the GI tract and then can be excreted with feces. This is one possibility.

There is another possibility, but specifically, as you know in the gut, we have our microflora. Of many functions of microflora, one is hydrolysis. Here is the hydrolysis of those glucoronide versions of the drugs. The microflora remove the glucuronide from the drug, frees up the drug. In the free form, the drug can be reabsorbed from the GI tract. Same as the drug ingested ends up in the same part of the intestine from which it is reabsorbed. Once the drug is reabsorbed, it can act again.

Thanks to the **gut flora, the drug can have a prolonged duration of action**. This is obviously included when the duration of action for the drug is calculated and when you decide about the drug dosing. One important drug rule that actually undergoes this enterohepatic cycling are all contraceptives. We'll come back to this when we talk about antibiotics and consequences of removing of some our indulgence microflora. As you can imagine, if you remove the microbes that are responsible for hydrolysis, the removal of the glucoronate groups were now longer happen, so the drug will not be able to enter the circulation and it's basically excreted. So the drug will have a shorter duration of action and this has actually some implications for your treatment treatment of your patients with antibiotics.
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NEXT SLIDE

Let's briefly talk about factors that affect drug metabolism. This is a really important topic with huge implications for understanding the mechanisms of drug interactions and also changed drug action under different systemic conditions. This is only an overview and will be coming back to us in separate sessions and also when we discuss the specific drug groups.

Genetic: as I already mentioned about phase one reactions by enzymes, non-microsomal enzymes are affected by genetic polymorphisms. Some of the enzymes that metabolize drugs can come in different forms with different levels of their inducing activity. Levels of the enzymes may differ from individual to individual. This is genetically determined. When you are dealing with the deficiency or the excess of the specific enzyme, you can expect different drug action. If you are talking about enzymes that activate the drug, such as activate the prodrugs, or make active metabolite when you have the deficiency of the given enzyme, you expect the lower activity of the drug. On the other hand, if the enzyme is responsible for inactivation of the drug, when you have a deficiency in the enzyme, you expect increased activity of the specific drug.

Blood flow: even though the liver is not is our primary organ of metabolism, the pulmonary metabolism can be really significant for some drugs because of the blood flow being greater for the lungs compared to the liver.

Protein building: for many drugs, when the drug is highly bound to plasma proteins, their metabolism is decreased, meaning the **binding decrease as a drug metabolism decrease**. The drug is safe from being metabolised from being from leaving their circulation, if it's bound to plasma proteins. So the consequences of decreasing the plasma protein levels or having drugs competing for binding sites. The consequence of this would be the greater amount of free drug, then increase drug metabolism.
Another possibility here that actually **increase drug binding can increase metabolism**. Increase binding, increase delivery of the drug which is already available there in the pool associated with the protein. If we are dealing with the drug, e.g. lidocaine, that there's a lot of enzyme. Their limitation is actually the delivery of the drug to the liver, By delivering with the protein, you increase the pool available for metabolism.

Know the conditions that can affect hepatic drug metabolism:
- DECREASE: age (neonatal, elderly), hypothyroidism, cirrhosis, heart failure, stress, inflammation, drugs, other factors that reduce hepatic blood flow.
- INCREASE: hyperthyroidism, uremia, chronic alcohol use.

Know drugs that INHIBIT drug metabolizing enzymes: (listed)
- Omeprazole: We already talked to this about the drug in the context of affecting drug absorption by changing the pH in the stomach. Pmeprazole is also known to inhibit an enzyme metabolism.
- Cimetidine which is actually even stronger inhabitant of drug metabolism.

Metabolism

Factors Affecting Drug Metabolism

1. **Genetics:** Amounts and types of drug metabolizing enzymes are determined genetically: up to 6-fold difference in the rate of drug metabolism among individuals ⇒ individual variation in drug response (e.g., Codeine/Morphine conversion – CYP2D6 deficiency or excess).
2. **Blood Flow (Drug Delivery):** Pulmonary metabolism may exceed the hepatic rate even with lower enzyme activity in the lungs because of greater blood flow (e.g., Fentanyl).
3. **Protein Binding:** ↑ Binding ⇒ ↓ Metabolism (e.g., Sulfonamides, Warfarin, Phenytoin);
   but also: ↑ Binding ⇒ ↑ Metabolism (limited by hepatic blood flow, e.g., Lidocaine)

Conditions that can affect Hepatic Drug Metabolism

DECREASE:

Age: Neonatal, Elderly (↓ enzymes)
Hypothyroidism (↓ synthesis of metabolic enzymes)
Cirrhosis, Heart Failure (↓ hepatic blood flow)
Stress, Inflammation (↓ free drug delivery)
Drugs and other factors (e.g. some infections) that reduce hepatic blood flow

INCREASE:

Hyperthyroidism (↑ synthesis of metabolic enzymes)
Uremia (↓ Albumin binding capacity;↑free drug delivery)
Chronic Alcohol use (induction of CYP enzymes)

Drugs that Inhibit Drug Metabolizing Enzymes

Erythromycin
Metronidazole
Sulfonamides
Ketoconazole
Fluoxetine (Prozac)
Amiodarone, Verapamil
Cimetidine (Tagamet), OTC
→ Omeprazole (Prilosec), OTC
Inhibitors of: Monoamine Oxidase (MAO) & Aldehyde Dehydrogenase (Disulfiram)
Ginkgo Biloba & Grapefruit Juice

Metabolism

QUINIDINE: inhibits that enzyme that's responsible for metabolism according to morphine

Factors Affecting Drug Metabolism (Cont'd)

Enzyme Inhibition

AMIODARONE: drug inhibitors of metabolic

- Competition for an isoenzyme by two drugs (if metabolized by saturation kinetics ⇒ capacity - limited metabolism, e.g. Phenytoin & Warfarin competing for CYP2C9);
- Drug inhibition of enzyme activity (Amiodarone-CYP3A4 /CYP2C9/CYP2D; Quinidine–CYP2D6);

*Inhibition of drug metabolism occurs in a dose-dependent manner and can precipitate **toxicity**.*

Microsomal Enzyme Induction

Drug interaction with DNA ⇒↑synthesis of enzyme protein ⇒
↑ activity of mixed-function oxidases (CYP) and UGT ⇒ ↑ rate of drug metabolism (2-4 X).
[e.g, Phenytoin, **Rifampin** – several CYP enzymes].

Induction takes from days to 2 weeks to reach its peak, compared to hours for enzyme inhibition.

Consequences of Enzyme Induction:

1. ↓ Intensity/Duration of action of drugs inactivated by metabolism;
2. ↑ Toxicity (↑ Synthesis of highly reactive intermediaries, e.g., Acetaminophen);
3. ↑ Pharmacokinetic Tolerance (a loss of drug responsiveness);
4. ↑ Metabolism of endogenous chemicals (e.g., Bilirubin, Steroids; Vitamin D ⇒ rickets and osteomalacia in epileptic patients treated with Phenytoin, etc.);
5. Acute Intermittent Porphyria (de-repression of d-aminolevulenic acid synthase ⇒ ↑porphyrin precursors).

Microsomal Enzyme Induction: the enzymes that are located in microsomal, those undergo induction, are susceptible to induction. This induction is mediated specifically by drugs. The drugs induce enzymes that are responsible for also metabolism of indulgent substances. Here we have both effect of induction on drug metabolism but also on metabolism antigen substances.

- **Rifampin** (This is a drug used to treat tuberculosis) and **phenytoin** will be antiepileptic drug. Both are known as strong inducers. Phenytoin is the one that's classically used on exams. Rifampin is stronger (probably one of the strongest) drugs that induce enzymes.

CONSEQUENCES OF ENZYME INDUCTION:

- **Decrease intensity/duration of action of drugs inactivated by metabolism.** If the enzyme causes inactivation of the drug, when you induce the enzyme, the drug is metabolised faster. This decreases intensity or duration of the drug action.
- **Increase toxicity:** We talk about specifically acetaminophen. It's safe drug except for overdose because this can overwhelm the glutathione reaction. That will actually neutralize those highly toxic metabolites and those highly reactive intermediate metabolites and can cause serious toxicity. For example, liver damage. When you induce the enzyme, there's a lot of drug metabolise a system that most of action is overwhelmed. Those intermediate forms of metabolites can be very toxic. If are not taken care of by the body, this can lead to, like in the case of acetaminophen, the liver damage and so toxicity.
- **Increase pharmacologic tolerance:** So when you induce that enzyme that inactivates the drug, the drug is inactivated more quickly. They lack of effect of the drug or decreased responsiveness or effect of the drug. This will be the pharmacokinetic tolerance. You can put a lot of drug in the body and you don't see the effect. The body tolerates the drug without you know responding in any way.
- **Increase metabolism of endogenous chemical:** Vitamin D in epileptic patients that treated with phenytoin when you activate the enzymes that are also responsible for the metabolism of vitamins for example.
- Some drugs side effects are **acute intermittent porphyria**. This is because of the precursors being at the increased levels.

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NEXT SLIDE

A vast majority of drugs are excreted through the kidney. This has important clinical implications for patients with kidney disease where the drug exclusion may be compromised. If the drug is excreted in its original form, not metabolised, this could lead to increased duration of drug action with potential risk of toxicity. If you don't consider the increased excretion time, and the dosing of the drug is too frequent, or if we're talking about drugs that are metabolised to metabolites, that could be potentially toxic. In general, kidney disease it can lead to all sorts of problems we have processing of drugs if the excretion is compromised.

In addition to the kidney, there are other routes potential routes of drug excretion.

Biliary excretion: besides the enterohepatic cycling, you have drugs that maybe are not cycled through the system several times, but they are actively imported to the bile and can be excreted through that intestine w the feces.

Pulmonary Excretion

Excretion by Breast Milk:
Highly lipid soluble drugs would passively diffuse to the breast milk and then available for the infant. Obviously this will be the negative consequence. The milk pH is lower than plasma pH plasma. Now we are dealing with a more acidic environment. Weak base drugs that are basic drugs in the acidic environment. They will be more ionzied, so they basically get trapped. They are more concentrated. You expect higher concentration in the breast milk of drugs that are weak bases.

Excretion

Quantitatively, the KIDNEY is the major organ of drug excretion. Other clinically significant routes include BILIARY, PULMONARY and BREAST MILK excretion.

Biliary Excretion

Active transport of **Free Drug** and **Drug Metabolites** (**Phase II,** particularly **Glucuronides**):
Plasma → Hepatocytes → Bile (→→→ Intestine→ Feces).
DRUGS: Erythromycin, Ampicillin, Rifampin, Tetracycline, Oral Contraceptives.

Enterohepatic Recycling (Drugs/Drug Metabolites: Bile → Intestine → Plasma → Hepatocytes.)
can **prolong the duration of drug action** *
until the system is interrupted
(e.g., Antibiotics, reduction of bile flow) ⇒ Excretion in Feces.

→ when they swallow the saliva

Similarly, drugs excreted through saliva are available for reabsorption from the GI tract.

Pulmonary Excretion

A primary route for the elimination of gases and volatile liquids (e.g., general anesthetics, alcohol), driven by **partial pressure in the blood**, independent of lipid solubility.

Excretion by Breast Milk

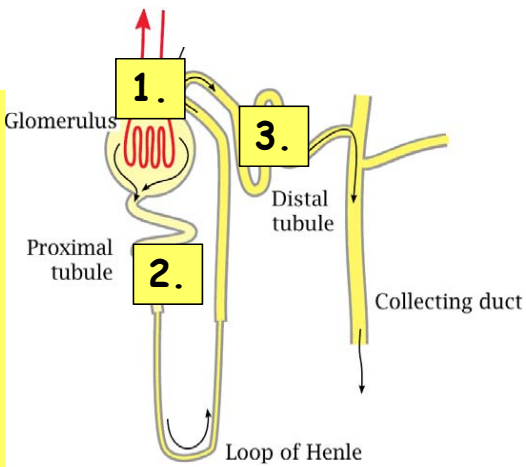
Elimination of drugs by breast milk represents a potential danger to the nursing infant.
The primary variable determining the passage of drugs into milk (mostly by passive diffusion) is **lipid solubility**.
Milk pH (7.0) < Plasma pH ⇒ Basic Drugs are more concentrated.
Drugs of particular concern include Lithium, Anticancer Agents & Isoniazid.

3 types of processes that are going on in the kidney that contribute to drug excretion both positively and negatively. Glomerular filtration and tubular secretion both increased drug excretion. There is also a possibility of tubular reabsorption of drugs. Reabsorption actually decreases drug excretion. As you imagine, the drug is reabsorbed back to the system. The drug is metabolite.

Excretion

Renal Excretion

[Glomerular Filtration] + [Tubular Secretion] – [Tubular Reabsorption]



1. Glomerular Filtration (Passive)

Plasma-bound drug is not filtered.
All free drug (lipid soluble or insoluble) is filtered.
Glomerular filtration of a drug depends on renal blood flow.
GFR declines progressively after the age of 50.

2. Tubular Reabsorption (Passive)

A) **Lipid soluble** drugs get **reabsorbed** (along with 99% of the filtrate).
B) Lipid insoluble/highly ionized drugs are not reabsorbed.
C) **Weak electrolyte** reabsorption is **urinary pH-dependent**:
weak bases less reabsorbed (more ionized) in acidic urine;
weak acids less reabsorbed (more ionized) in alkaline urine.

3. Tubular Secretion (Active)

Transfer of organic acids and bases by non-specific transporters.
Plasma protein binding of a drug may facilitate excretion by secretion (unlike binding to extravascular tissues).

Age Dependence

Tubular transport is not well developed at **birth** ⇒ **longer duration** of drug action (e.g., Penicillin, Aspirin).

The renal clearance of many drugs is substantially decreased above 75 years of age.

GLOMERULAR FILTRATION: Passive and effect all the drugs. except the pool that's bound to plasma proteins. Plasma proteins are not filtered during the filtration. In the primary filtrate and in healthy kidney, you do not have proteins. So the drugs that are plasma protein bound are also not filtered. But all free drug, whether it's lipid soluble or insoluble, is filtered. Filtration depends on the renal blood flow. So decreasing the renal blood flow would decrease the drug excretion. Also, kidney failure, or basically decreased remove filtration rate, would affect the drug excretion. GFR actually declines after the age of 50. You can have a patient who is as young as 50+, consider the compromise drug excretion potentially. Then, with consequences for drug toxicity or longer duration of action, if metabolite that's excluded, you should consider toxicity. If drug is excreted in unchanged form original drug, then this will prolong the drug action.

TUBULAR REABSORPTION: Passive the re-absorption of the drug but passively through the membranes are the same rules as drug absorption.

TUBULAR SECRETION: Active ~drug is bound to plasma proteins cannot be metabolized. For most drugs, it cannot be filtered here for the glamour of filtration of drugs. BUT drugs that are bound to proteins can be secreted more easily because the available there in the tubule to be taken by the transporter and removed. New poll is waiting, ready to be bound to the transporter to be removed from the body.

If you have a patient 75 years old or older, you have to seriously consider increased duration of drug action or increased drug toxicity