Pharmacology

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ARKAN ACADEMY

Biotransformation

- Xenobiotics: Foreign compounds including drugs, industrial and environmental toxins
  - It enters the body by the GI, skin and lungs
  - To be excreted by the kidney if they are small and polar or ionized at the physiological pH
  - Lipophilic drugs can be reabsorbed in the glomeruli, so they must be metabolized into more polar molecules in the liver

- Metabolism of drugs usually produce less active (or even inactive) molecules than the parent drug but some drugs can:
  - Have enhanced activity
  - ***Prodrug:*** Inactive and must be activated such as levodopa and codeine
  - Produce toxicity, such as:
    - ✓ ***Paracetamol*** (acetaminophen) may be converted to hepatotoxin N-acetyl-p-benzoquinone imine
    - ✓ ***Halothane*** is metabolized to free radicals that are hepatotoxic

- Biotransformation involves 2 Phases to convert a drug into a more polar metabolite to be excreted

1. Phase I

- Metabolism is done by ***introducing*** or ***unmasking*** a functional group (OH, NH_2, SH)
- These metabolites can be inactive, less active or more active than the parent compound
- Phase 1 reactions include:
  - ***Oxidation*** mainly by the microsomal mixed function *oxidase* system, *cytochromes P450* enzymes
  - ***Epoxidation*** and ***aromatic hydroxylation (N, O, S)***
  - ***Deamination***, ***desulfuration*** and ***dechlorination***
  - ***Reduction*** reactions may be *cytochrome P450* dependent systems or *dehydrogenase* and *reductase*
  - ***Hydrolysis*** of esters and amides by *esterase* and *amidase*, respectively
  - ***Dealkylation (unmasking)***

- Cytochrome P450 enzymes metabolize lipid-soluble drugs and it is located in the *endoplasmic reticulum*
  - It has many P450 isozymes, where the most important of them are *CYP1A2*, CYP2A6, CYP2B6, CYP2C8, *CYP2C9*, CYP2C18, CYP2C19, *CYP2D6*, CYP2E1, and *CYP3A4*
  - ***CYP3A4*** alone is responsible for the metabolism of ***more than 50%*** of drugs in the liver

2. Phase II

- Involve the ***conjugation*** with endogenous substrates to yield a drug conjugate
  - These conjugates are polar and inactive
- These reactions are synthetic reactions involving transferases and high-energy intermediates

Type of Conjugation	Endogenous Reactant	Transferase (Location)
Glucuronidation	UDP glucuronic acid	UDP glucuronosyltransferase (microsomes)
Acetylation	Acetyl-CoA	*N*-Acetyltransferase (cytosol)
Glutathione conjugation	Glutathione (GSH)	GSH-*S*-transferase (cytosol, microsomes)
Sulfation	Phosphoadenosyl phosphosulfate	Sulfotransferase (cytosol)
Methylation	*S*-Adenosylmethionine	Transmethylases (cytosol)

- Examples of conjugation:
  - ***Uridine 5'-diphosphate [UDP]-glucuronosyl transferases (UGTs)*** are the <u>most dominant</u> conjugating enzymes
    - ✓ Groups ***glucuronidated*** are –OH, -NH, -SH, -COOH, -NHOH
  - ***Sulfotransferases (SULTs)*** use ***3'-phosphoadenosine 5'-phosphosulfate (PAPS)***
    - ✓ Inorganic sulfate is a limiting factor for sulfation where its sources is food and sulfur-containing amino acids
    - ✓ Almost all chemical groups that are glucuronidated are also sulfated
    - ✓ ***Infants*** are more capable of ***sulfation***, but ***glucuronidation*** predominates in ***adults***
  - ***N-acetyltransferases (NATs)*** utilize ***acetyl CoA*** as the endogenous cofactor for conjugation
  - ***Glutathione (GSH) transferases (GSTs)***
    - ✓ Uses ***glutathione (GSH)*** which consists of Glu-Cys-Gly, which is a nucleophile that detoxify electrophile causing *halogen replacement* (R-Cl ➔ R-SG)
    - ✓ It conjugates *epoxides*
    - ✓ These conjugates may appear in **<u>bile</u>** but not in urine
    - ✓ They are metabolized further to ***cysteine conjugates*** and then to ***mercaptouric acid conjugates*** (N-acetylated cysteine conjugates), that appear in **<u>urine</u>** by an active transport process
  - ***S-Adenosyl-L-methionine (SAM)*** mediate O-, N-and S-methylation of drugs and xenobiotics by ***methyltransferases (MTs)***

- Certain conjugation reactions may lead to formation of reactive species and drug toxicities, such as:
  - ***Acyl glucuronidation*** of *nonsteroidal anti-inflammatory drugs (NSAIDs)*
  - ***O-sulfation*** of *N-hydroxy-acetylaminofluorine*
  - ***N-acetylation*** of *isoniazid*
  - ***Sulfation*** leads to activation of the prodrug *minoxidil*
  - Morphine-6-***glucuronide*** is more potent than *morphine*

- Paracetamol undergoes glucuronidation and sulfation, which make up 95% of total excreted metabolites
- Paracetamol **overdose** can induce **<u>hepatotoxicity</u>**
  - A minor toxic metabolite (P450-dependent) may accumulate in case of paracetamol over dose, where this metabolite can be eliminated normally by GSH conjugation pathway to prevent hepatotoxicity
  - At high paracetamol dose and when GSH is depleted, the toxic metabolite accumulates resulting in hepatotoxicity
  - It can be solved by ***N-acetylcysteine (antidote)*** within 8-16 hours after the over dose
  - ***Administration of GSH is not effective*** because it does not cross cell membranes readily

- Enzyme Induction
  - It means enhanced rate of enzyme synthesis, or reduced rate of degradation
  - Results in *accelerated drug metabolism*, and usually in a *decrease in the pharmacological action*
  - It can cause toxicity if metabolism caused reactive molecules
  - Induction mostly starts at the gene level
- Inducers include:
  - Environmental chemicals and pollutants such as *polycyclic aromatic hydrocarbons* present in *tobacco smoke* and *charcoal-broiled meat*
  - Drugs: *barbiturates*, *phenytoin*, *carbamazepine*, *rifampin*
  - *Cruciferous vegetables* and *St. John's wort*
- **Autoinduction** can cause tolerance to the drug action such as ***carbamazepine***

Induction and inhibition involve drug-drug interactions

- Enzyme Inhibition can be caused by:
  - *Macrolide antibiotics* such as *erythromycin*, inactivate (CYP3A)
  - *Suicide inhibitors* (inactivators) include grapefruit furanocoumarins
  - *Substrates compete* with each other for the same active site of the enzyme
  - *Deficiency of cofactors* impair drug metabolism
  - *Inhibitors of nucleic acid and protein synthesis* impair enzyme synthesis and, thus, drug metabolism.
  - *Malnutrition*.
  - *Impairment of hepatic* function.
- Inhibition can cause accumulation of drug in the body and increase the adverse effect (toxicity)
  - In case of prodrugs, there will be failure of drug response

Routs of administration

- It involves 3 main routs:

1. *Enternal (throught GI)*

- *Oral route (PO):* Most commonly used route
  - The drug should be swallowed
  - *Safest*, *most convenient*, and *most economical*
  - *Duodenum* is the major site of absorption, but stomach, jejunum and ileum may be involved
  - Its disadvantages are:
    - ✓ The patient must be ***cooperative and complaint***
    - ✓ ***Variable absorption*** affected by vomiting, first-pass, disintegration and dissolution failure, destruction (gastric acidity and normal flora), food and intestinal motility alteration, and splanchnic blood flow

- *Sublingual route (SL)*
  - Drug is placed under the tongue.
  - *Avoids first-pass* effect.
  - Used when a *rapid onset* is required – such as in angina pectoris
  - Not commonly used

- *Rectal route (PR)*
  - *Avoids first-pass* effect partially (~ 50%), used for unstable or poorly absorbed drugs in the GIT
  - Useful in *unconscious* or *vomiting* patients
  - Absorption is often ***irregular***, ***incomplete*** and ***unpredictable*** and can be used for a ***local effect***
  - Used for *rapid effect*.
  - Aseptic technique is not required

2. Parenteral Routes

- *Intravenous route (IV)*
  - Injection of an aqueous solutions into the venous blood (can be bolus or infusion)
    - ✓ Oily vehicles or those that precipitate blood constituents should NOT be given IV
  - *Rapid onset* of action
  - *No first-pass* hepatic metabolism, the drug goes first to the **right** side of the heart, the lung, the left side of the heart, then to the systemic circulation
  - Disadvantages include:
    - ✓ Produce high initial concentration of the drug that might be ***toxic***
    - ✓ ***Hard to control adverse effects*** because once injected, the drug reached the site of action

- *Intramuscular route (IM)*
  - The drug is injected within muscle fibers of deltoid, gluteus maximus or vastus lateralis
  - Absorption of drug ***depends on blood supply*** (**slower for g.m**)
    - ✓ Absorption is reduced in circulatory failure or shock
  - To be injected IM, the drug ***must be non-irritating*** to tissues
  - Can accommodate *large volumes*
  - It can utilize and use:
    - ✓ ***Aqueous solutions*** for fast absorption and *rapid* action
    - ✓ ***Depot preparations (suspensions)*** for slow, *sustained* absorption (oily vehicles, ethylene glycol)

- *Subcutaneous injections (SC, or SQ)*
  - The drug is injected under the skin where it should be non-irritating to tissues.
  - Absorption is affected by ***blood flow*** (Absorption is slow and *sustained*)
  - Accommodate ***smaller volumes*** than IM
  - *Solid pellets* can be implanted under the skin to produce effects over weeks-months

3. *Others*

- *Inhalational or pulmonary route*
  - Drugs are absorbed across pulmonary epithelium and mucous membranes of respiratory tract
  - Can be *gaseous or volatile* drugs, such as *general anesthetics*
  - Can also be used for *solids* that can be put in an *aerosol*, such as drugs for *bronchial asthma*
  - Absorption is *rapid* and *avoids first-pass* effect.
  - The lung acts as a route of elimination also

- *Topical application*
  - Used for a **local** effect on:
    - ✓ *Mucous membranes:* conjunctiva, nose, mouth, nasopharynx, oropharynx, vagina, rectum, colon, urethra, and urinary bladder
    - ✓ *Skin:* can be absorbed systemically in the cases of highly lipid-soluble drugs or abraded, burned and inflamed skin.

- *Transdermal route (TD)*
  - The drug is applied to the skin for systemic effect, such as in angina
  - For a *sustained* effect.
  - *Avoids first-pass* metabolism

Route	Bioavailability	Advantages	Disadvantages
Parenteral Routes			
Intravenous bolus (IV)	Complete (100%) systemic drug absorption. Rate of bioavailability considered instantaneous.	Drug is given for immediate effect.	Increased chance for adverse reaction. Possible anaphylaxis.
Intravenous infusion (IV inf)	Complete (100%) systemic drug absorption. Rate of drug absorption controlled by infusion rate.	Plasma drug levels more precisely controlled. May inject large fluid volumes. May use drugs with poor lipid solubility and/or irritating drugs.	Requires skill in insertion of infusion set. Tissue damage at site of injection (infiltration, necrosis, or sterile abscess).
Subcutaneous injection (SC)	Prompt from aqueous solution. Slow absorption from repository formulations.	Generally, used for insulin injection.	Rate of drug absorption depends on blood flow and injection volume. Insulin formulaton can vary from short to intermediate and long acting.
Intradermal injection	Drug injected into surface area (dermal) of skin.	Often used for allergy and other diagnostic tests, such as tuberculosis.	Some discomfort at site of injection.
Intramuscular injection (IM)	Rapid from aqueous solution. Slow absorption from nonaqueous (oil) solutions.	Easier to inject than intravenous injection. Larger volumes may be used compared to subcutaneous solutions.	Irritating drugs may be very painful. Different rates of absorption depending on muscle group injected and blood flow.
Intra-arterial injection	100% of solution is absorbed.	Used in chemotherapy to target drug to organ.	Drug may also distribute to other tissues and organs in the body.
Intrathecal Injection	100% of solution is absorbed.	Drug is directly injected into cerebrospinal fluid (CSF) for uptake into brain.	
Intraperitoneal injection	In laboratory animals, (eg, rat) drug absorption resembles oral absorption.	Used more in small laboratory animals. Less common injection in humans. Used for renally impaired patients on peritoneal dialysis who develop peritonitis.	Drug absorption via mesenteric veins to liver, may have some hepatic clearance prior to systemic absorption.
Enteral Routes			
Buccal or sublingual (SL)	Rapid absorption from lipid-soluble drugs.	No "first-pass" effects. Buccal route may be formulated for local prolonged action. Eg, adhere to the buccal mucosa with some antifungal. Buccal is different from sublingual which is usually placed "under tongue."	Some drugs may be swallowed. Not for most drugs or drugs with high doses.
Oral (PO)	Absorption may vary. Generally, slower absorption rate compared to IV bolus or IM injection.	Safest and easiest route of drug administration. May use immediate-release and modified-release drug products.	Some drugs may have erratic absorption, be unstable in the gastointestinal tract, or be metabolized by liver prior to systemic absorption.
Rectal (PR)	Absorption may vary from suppository. More reliable absorption from enema (solution).	Useful when patient cannot swallow medication. Used for local and systemic effects.	Absorption may be erratic. Suppository may migrate to different position. Some patient discomfort.
Other Routes			
Transdermal	Slow absorption, rate may vary. Increased absorption with occlusive dressing.	Transdermal delivery system (patch) is easy to use. Used for lipid-soluble drugs with low dose and low MW (molecular weight).	Some irritation by patch or drug. Permeability of skin variable with condition, anatomic site, age, and gender. Type of cream or ointment base affects drug release and absorption.
Inhalation and intranasal	Rapid absorption. Total dose absorbed is variable.	May be used for local or systemic effects.	Particle size of drug determines anatomic placement in respiratory tract. May stimulate cough reflex. Some drug may be swallowed.

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