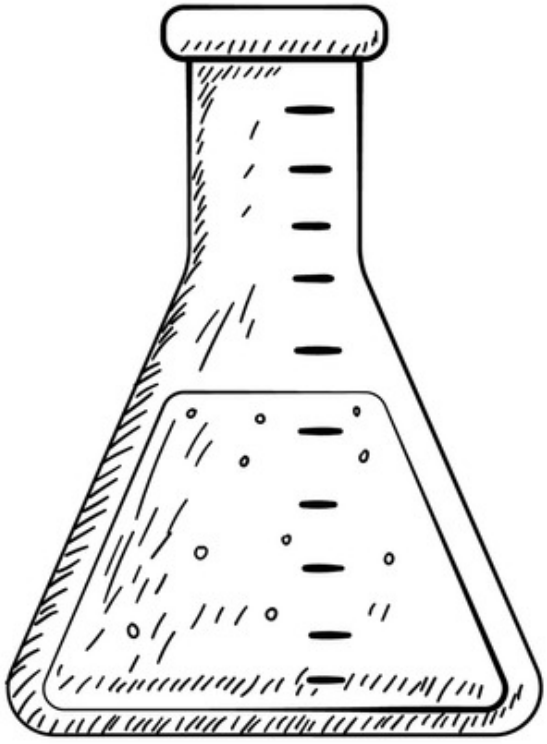
General Pharmacology



USMLE PULSE

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Pharmacokinetics and Dynamics

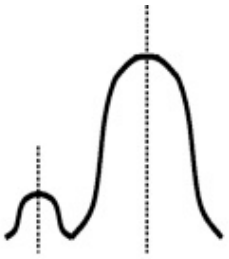
1.**Cytochrome P450 (CYP) enzymes** are a group of heme-containing proteins that are responsible for the majority of drug metabolism, which occurs predominately in the liver. Various CYP subtypes exist, with **CYP3A, CYP2D, and CYP2C** as the most active subtypes involved in drug metabolism. These enzymes generally function to deactivate drugs and facilitate excretion from the body **by improving water solubility**. However, **they also metabolize certain compounds to their active forms**.

Polymorphisms may occur in the genes coding for these enzymes, altering their expression or activity. Three important phenotypes exist: **poor, intermediate, and rapid metabolizer**. Identifying these variations on an individual basis provides a framework for optimizing therapy, predicting treatment efficacy, and minimizing toxicity.

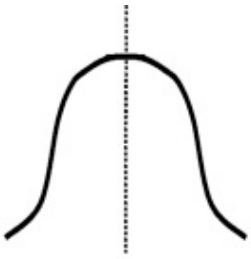
Tamoxifen, a selective estrogen receptor modulator used in the treatment of estrogen receptor-positive breast cancer, is a prodrug metabolized by CYP2D to its active metabolite, **endoxifen**. Patients with genetic polymorphisms resulting in poor CYP2D activity are exposed to decreased levels of the active metabolite and have a higher risk of disease relapse.

Cytochrome P450 can also found in club cells of Bronchi.

2)The rate and extent of drug metabolism normally varies from person to person. These slight interpersonal variations in the ability to metabolize drugs are typically reflected graphically by a unimodal distribution, usually in the shape of a bell curve, when plasma levels of drug are measured at a fixed time following a fixed dose of drug. With most drugs, the majority of people fall within one standard deviation and 95% of people fall within two standard deviations of the population mean of plasma concentration. A single peak in this type of graph indicates that the population being tested possesses a similar genetic drug metabolizing capacity.



Bimodal phenotype distribution typically resulting for drug metabolizing enzyme polymorphisms



Unimodal phenotype distribution typical of drug target gene polymorphism

A bimodal (discontinuous, polymorphic) curve results from the presence of two apparently distinct groups within the study population and suggests a pharmacogenetic polymorphism in drug metabolizing capacity. In other words, the two peaks indicate two sets of responders to the drug within the

population: one that rapidly converts the drug into its metabolite (considered normals) and another that converts the drug slowly, leading to accumulation of the original drug in the plasma.

3)The study results show that the cerebral spinal fluid (CSF) viral load level remains elevated when subjects are treated with Drug X alone but becomes undetectable when Drug X is combined with the adjuvant agent. Because average serum levels are relatively equal between the 2 groups, it is likely that the adjuvant improves the efficacy of Drug X by increasing its ability to penetrate the blood-brain barrier (BBB).

Many drugs have a difficult time crossing the BBB due to the presence of specialized endothelial cells with **very tight intercellular junctions** that form a physical barrier separating the CNS from the circulation. In addition, multidrug transport proteins, particularly **p-glycoprotein,** are highly expressed on the luminal membrane of brain capillary endothelial cells. P-glycoprotein is an ATP-driven efflux pump that actively removes a wide range of substrates from cells, including many commonly prescribed drugs (eg, antibiotics, immunosuppressant agents, HIV protease inhibitors).

In HIV infection, poor penetration of antiretroviral medications allows the brain to act as an anatomical sanctuary where viral replication can proceed unchecked, facilitating the development of resistant strains. Methods of bypassing the BBB (eg, disruption of tight junctions, p-glycoprotein inhibition) can improve drug delivery to the CNS. **P-glycoprotein** transporters are also found on the apical surface of enterocytes and can limit drug bioavailability by pumping the drug back into the intestinal lumen. However, inhibition of p-glycoprotein can have a variable effect on serum drug levels, as increased bioavailability is often countered by increased drug distribution (eg, into the CSF or intracellular compartments).

4)The kidney is the primary site of excretion of most drugs, with or without prior chemical modification in the liver. The liver is the major site of drug biotransformation and metabolism, but some drugs are also predominately eliminated by the liver into the bile and feces. Drugs with high intrinsic hepatic clearance tend to have high lipophilicity and a high volume of distribution. **Highly lipophilic drugs tend to be poorly eliminated in the kidney as these agents rapidly cross tubular cell membranes after filtration to reenter the tissues**.

High lipophilicity (lipid solubility) allows the drug to cross cellular barriers more easily and enter hepatocytes. It can then be excreted in the bile or through other methods of elimination. In addition, high lipid solubility

assures a wide distribution to many different tissues including the brain, liver, and adipose tissue.

5.Heart failure can cause changes in pharmacokinetic parameters that can alter drug effectiveness and lead to increased toxicity. **Decreased cardiac output leads to tissue hypoperfusion, lowering the volume of distribution of many drugs and reducing perfusion of organs responsible for drug clearance (eg, liver, kidneys)**. This can result in **higher serum drug levels and a prolonged elimination phase**, which can be particularly important for drugs with a narrow therapeutic index (eg, digoxin, antiarrhythmics).

6)

Common medications to avoid in older adults (Beers criteria)	
Anticholinergic	First-generation antihistamines Gastrointestinal antispasmodics
Cardiovascular	Alpha-1 blockers (as antihypertensives) Centrally acting alpha-2 agonists Many antiarrhythmics
CNS	Tricyclic antidepressants Antipsychotics Barbiturates, benzodiazepines & other hypnotics
Endocrine	Long-acting sulfonylureas Sliding-scale insulin
Pain	Nonselective NSAIDs Skeletal muscle relaxant

7)Drug distribution is not uniform; the rate at which drugs are delivered to target tissues is dependent on several factors, such as regional blood flow and drug characteristics. **The pharmacokinetic profile of highly lipophilic anesthetic drugs, such as propofol, can be predicted using a multi-compartment model of distribution.** Following administration of a single intravenous bolus, drug levels are high in the central compartment (ie, plasma). However, the drug is quickly distributed to the well-perfused peripheral compartment (eg, brain, liver, kidneys, lungs) due to the increased lipophilicity of the tissues compared to the blood.

Over time, drug redistribution will occur through the central compartment into the poorly-perfused peripheral compartment (eg, skeletal muscle, fat, bone), which has the highest volume of distribution for lipophilic

agents. Redistribution occurs rapidly with highly lipophilic drugs and is responsible for the short duration of action seen with commonly used anesthetics such as propof

Autonomic

Sympathomimetics

1. Norepinephrine

A.Development of **venous blanching along with induration** and pallor of the tissues surrounding the norepinephrine infusion site are signs of norepinephrine extravasation. The norepinephrine leak causes intense α1 receptor mediated vasoconstriction which can lead to local tissue necrosis. Such necrosis can be prevented by infiltration (using a syringe with a fine hypodermic needle) throughout the affected area with **phentolamine,** an α receptor blocker leading to vasodilatation (thus counteracting the vasoconstrictive effects of norepinephrine). This antidote must be given within 12 hours of extravasation to be effective.

B. Norepinephrine, an adrenergic agonist, is the preferred pharmacologic treatment for septic shock as it predominately stimulates a1, a2, and B1 receptors, with little influence on B2 receptors. This leads to the following clinical effects:

- Stimulation of α1 adrenoreceptors leads to vasoconstriction in the skin and viscera, resulting in **increased systolic and diastolic blood pressure with decreased renal and hepatic blood flow**.
- Stimulation of β1 adrenoreceptors within the heart leads to increased cardiac contractility, conduction, and heart rate. However, the direct effect of norepinephrine on heart rate is counteracted by an indirect, baroreceptor-mediated reflex bradycardia that occurs following the increase in peripheral resistance. The combined result of these effects is often an unchanged or even decreased heart rate.
- Stimulation of α2 adrenoreceptors causes a decrease in cAMP in pancreatic β cells and in the intestines, resulting in decreased insulin secretion and reduced intestinal motility. **Central α2 adrenoreceptors are not stimulated by intravenous administration of norepinephrine as the molecule does not cross the blood-brain barrier**.

2.Phenylephrine is a selective alpha-1 adrenergic receptor agonist that causes vasoconstriction and increased blood pressure by increasing inositol trisphosphate (IP3) levels in vascular smooth muscle cells. The abrupt increase in blood pressure triggers a baroreceptor reflex, resulting in increased parasympathetic and decreased sympathetic outflow to the heart and vasculature.

The baroreceptor reflex–driven changes in the heart are mediated by beta-1 adrenergic receptors and muscarinic-2 receptors. Both reduced sympathetic stimulation of beta-1 receptors and increased parasympathetic stimulation of muscarinic-2 receptors trigger a decrease in cyclic AMP (cAMP) levels,

which leads to a decrease in heart rate and contractility to reduce cardiac output and lessen the increase in blood pressure. The reduction in heart rate is driven in part by decreased inward calcium current during phases 4 and 0 of the sinoatrial node action potential.
The above baroreceptor response also affects vascular smooth muscle, which is mostly under sympathetic control. Although this response causes reduced sympathetic stimulation of vascular alpha-1 receptors, the infusion of phenylephrine still maintains IP3 activity above baseline, resulting in a persistent vasoconstrictive effect.In contrast, an abrupt decrease in blood pressure triggers the opposite regulatory response via the baroreceptor reflex.Drugs that increase blood pressure by increasing SVR are called pressors and are most useful in treating septic shock

Sympatholytics

1)Beta-blockers

A)Patient with elevated blood pressure, tachycardia, palpitations, and anginal pain following **recent discontinuation of metoprolol** is most likely experiencing **beta blocker withdrawal syndrome**.

With changes in environmental stimulus, the feedback mechanisms in cells adjust the density of cell surface membrane receptors to regulate sensitivity to the stimulus. Prolonged beta-adrenergic blockade, for example, stimulates an increase in surface membrane expression of beta-adrenergic receptors, a process called upregulation. When beta-adrenergic blockade is abruptly withdrawn, the increased density of beta-adrenergic receptors creates an amplified response to circulating catecholamines (ie, increased sensitivity).

Because metoprolol is cardioselective and primarily blocks beta-1 receptors, abrupt cessation stimulates beta-1 receptor–mediated increased heart rate and cardiac contractility. There is also increased blood pressure due to increased cardiac output. These changes create increased oxygen demand that may cause ischemia (evidenced by ST depression on ECG) and trigger angina in patients with underlying coronary artery disease

B) **non-cardioselective beta blockers** (eg, propranolol, nadolol) can trigger bronchospasm in patients with underlying obstructive lung disease (asthma, chronic obstructive pulmonary disease [COPD]) due to beta-2 receptor blockade and should be avoided

Cardioselective beta blockers with predominant action on beta-1 receptors (eg, metoprolol, atenolol, bisoprolol, nebivolol) are safe in patients with stable obstructive lung disease and are the beta blocker of choice in these patients.

Combined beta and alpha receptor blockers (eg, carvedilol, labetalol) are also well tolerated and have been used safely in patients with COPD..

Adverse Effects

1.

Example mechanisms of tachyphylaxis	
Adrenergic agonists	Receptor inactivation & internalization by arrestins
Indirect sympathomimetics	Depletion of catecholamines from nerve terminals
Nitrates	Depletion of reduced thiols decreases mtALDH activity & NO production
Desmopressin (vWD)	Depletion of vWF from endothelial storage sites
Barbiturates	Induction of CYP450 enzymes

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2.

Chelation drug interactions	
Mechanism	Formation of insoluble compounds with polyvalent cations in the gastrointestinal tract Decreased absorption of drug
Commonly involved drugs	Tetracyclines Fluoroquinolones Levothyroxine
Chelation cations	Iron Calcium Magnesium Aluminum

3

Common medications that cause hyperkalemia	
Medication	Mechanism
ACE inhibitor, ARB	Decreases aldosterone secretion (inhibition of AT II/AT II receptor) + inhibits ENaC
Cyclosporine	Blocks aldosterone activity
Digitalis	Inhibits Na+/K+-ATPase
Heparin	Blocks aldosterone production
Nonselective	Interferes with β2-mediated intracellular

β-adrenergic blocker	potassium uptake
NSAID	Decreases renal perfusion → decreased potassium delivery to the collecting ducts
Potassium-sparing diuretic	Inhibits ENaC or aldosterone receptor
Succinylcholine	Causes extracellular leakage of potassium through acetylcholine receptors
Trimethoprim	Inhibits ENaC
ARB = angiotensin II receptor blocker; AT = angiotensin; ENaC = epithelial sodium channel; Na+/K+-ATPase = sodium-potassium pump; NSAID = nonsteroidal anti-inflammatory drug.	