Session 2: Pharmacodynamics I and II (*4 questions*)

Pharmacodynamics – what does the drug does to the body
- Action upon receptors

Affinity – ability to bind with the receptor
- k_d – dissociation constant; measure of drug **affinity** for the receptor (increased k_d = decreased affinity)

Potency – concentration (or dose) needed to achieve a given level of response (EC_{50})
- EC_{50} – concentration required to achieve half-maximal effect, equal to k_d

Efficacy – ability to activate a receptor (induce a functional change)
- E_{max} – the maximal response; measure of intrinsic activity (**efficacy**) of the drug
- *Note*: Compared to potency, efficacy is the more decisive factor in the choice of the drug

Characteristic features of the dose-response curve:
- Upper limit – index of drug **efficacy**, the maximal response that can be elicited by the drug
- Slope
  - Steep – moderate increase in dose *markedly increases* the response
    - High **efficacy** (high intrinsic activity) -> need individualized dosing
  - Flat – a *wide* dose range results in similar responses (standard dosing)
- Position of the dose axis
  - Leftward = higher **potency**
  - Rightward = lower **potency**

Specific – one receptor -> one effect (*unrealistic*)
Non-selective – one drug will work on *other* receptors, regardless of concentration -> *other* effects
Selective – high enough concentration of one drug will work on *other* receptors -> *other* effects
- The extent of separation of dose-response curves of a drug for different effects is a measure of its selectivity (greater separation = more selective)
  - Example) NSAIDs
    - Celecoxib = selective inhibitor of the inducible COX-2 isoform (greater separation)
    - Ibuprofen = non-selective inhibitor of COX-1 and COX-2 (less separation)

Therapeutic range – window between minimum therapeutic dose and minimum toxic dose
- Minimal therapeutic effect (receptor A1) achieved with minimum therapeutic dose
- Maximal acceptable adverse effect (receptor A2) achieved with minimum toxic dose

Therapeutic index = median toxic dose (TD_{50})/median effective dose (ED_{50})
- Expresses the safety margin of a drug (greater index = safer)

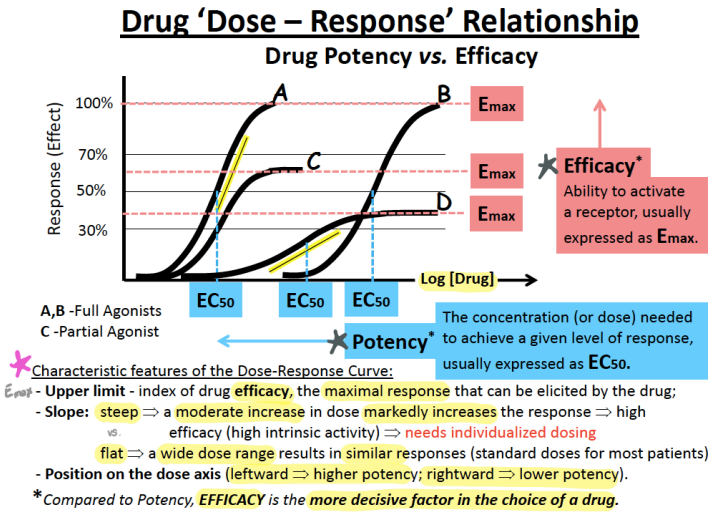
Synergism – action of one drug is increased by another
- **Additive** – effect of drugs A+B = effect of drug A + effect of drug B
- **Supra-additive (potentiation)** – effect of drugs A+B > effect of drug A + effect of drug B

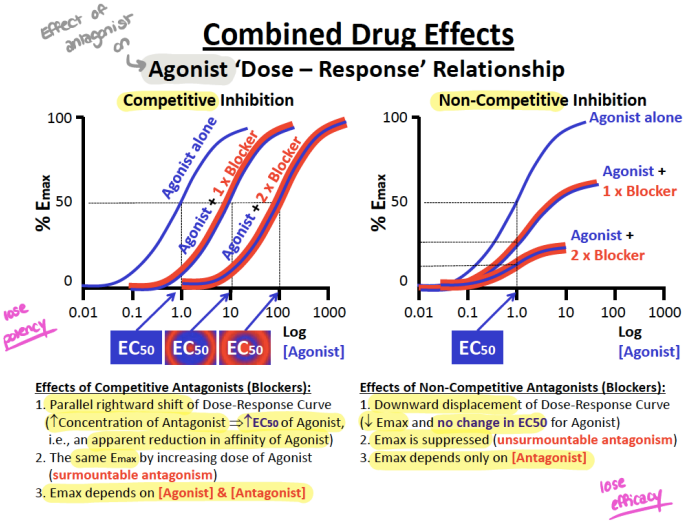
Antagonism – when one drug decreases or abolishes the action of another
- **Physical** – based on the physical property of the drug
- **Chemical** – two drugs react chemically, forming an active product
- **Functional (physiological)** – two drugs act on different receptors (by different mechanisms), but have the opposite overt effect on the same physiological function
- **Receptor-based** – one drug (antagonist) block the receptor action of the other (agonist); same receptor
  - Can be **competitive** or **non-competitive antagonism**

Competitive	Non-competitive
Attaches selectively and <u>prevents agonist binding</u>	Allows the agonist binding to the receptor, but <u>prevents receptor activation</u> by the agonist
Chemically <u>similar</u> to agonist; competes with agonist	Chemically <u>unrelated</u> to agonist; does not compete with agonist
Binds *<u>reversibly</u>* to the same site (exclusion of agonist molecules)	Binds *<u>irreversibly</u>* (it need not be a covalent modification of the receptor) to the same or a different (allosteric) site
<u>Prevents</u> conformational changes/signal transduction	<u>Alters</u> the receptor such that it is unable to bind the agonist or transduce the response
Lose **potency (increased EC_{50}, k_d)** - Parallel, rightward shift of DRC - No change in E_{max}	Lose **efficacy (decreased E_{max})** - Downward displacement of DRC - No change in EC_{50}

Regulation of Receptors

- In tonically active receptor systems, prolonged receptor *<u>inhibition</u>* (e.g., denervation/agonist deprivation, use of an antagonist) will lead to…
  - 1) Receptor <u>upregulation</u> = recruitment of internalized receptors, de novo synthesis
  - 2) <u>Amplification</u> of signal transduction
    - = **sensitization** = super-sensitivity of the receptor and effector system to the agonist
- Continued intense receptor *<u>stimulation</u>* (e.g., by the agonist) will lead to…
  - 1) Receptor <u>downregulation</u> = internalization, decreased synthesis, increased degradation
  - 2) <u>Attenuation</u> of signal transduction
    - = **desensitization** = refractoriness of the receptor to the agonist (becomes less sensitive)
    - = **pharmacodynamic tolerance** = loss of drug action/decrease in drug response (in relation to receptor)





Session 3: Clinical Case Scenario #1 (1-2 questions)

1. Oxybutynin (a competitive, muscarinic antagonist) would have the following pharmacodynamic effect on Pilocarpine (muscarinic agonist):
   a. Increase potency – *competitive antagonist = decrease potency*
   b. **Increase EC50** – *competitive antagonist = decrease potency = increase EC50*
   c. Decrease kd – *competitive antagonist = decrease potency = increase kd*

    d. Increase Emax – *competitive antagonism = no change in Emax*
    e. Decrease Emax – *competitive antagonism = no change in Emax*
2. In ONE WORD: a CONTRAINDICATION to treatment with Pilocarpine in this patient is:
    a. Asthma – due to receptor interaction in the lungs (muscarinic agonist vs antagonist)
3. In ONE WORD: the most likely reason for Propranolol withdrawal in this patient is:
    a. Asthma – ultimate goal is bronchodilation by stimulation of beta-2-adrenergic receptor
        i. Propranolol blocks beta-2 receptors (antagonist), which would prevent bronchodilation
4. Propranolol, a non-selective beta-adrenergic antagonist, is expected to have the following effect on Albuterol or Salmeterol, beta-2-adrenergic agonists:
    a. Decrease efficacy and decrease potency
    b. Decrease efficacy and increase kd
    c. Decrease efficacy and decrease EC50
    d. Only decrease efficacy
    e. **Only increase EC50**
        i. *Competitive receptor-based antagonism = decreased potency, same Emax (efficacy)*
        ii. *Decreased potency = increase EC50, kd*
5. Pilocarpine, a muscarinic agonist, is expected to have the following effect on Oxybutynin, a muscarinic antagonist:
    a. No effect on either efficacy or potency
    b. Decrease efficacy – receptor-based antagonism
    c. Decrease efficacy – physiological antagonism
    d. Increase potency – receptor-based antagonism
    e. **Decrease potency – receptor-based antagonism**
        i. *Competitive receptor-based antagonism = decreased potency, same Emax (efficacy)*
6. Pilocarpine, a muscarinic agonist, is expected to have the following effect on Albuterol or Salmeterol, beta-2-adrenergic agonists:
    a. No effect on either efficacy or potency
    b. Decrease efficacy – receptor-based antagonism
    c. **Decrease efficacy – physiological antagonism**
        i. *Muscarinic agonist vs beta-2 adrenergic agonist = opposite physiological effects, but different receptors (not receptor-based antagonism*)
    d. Increase potency – receptor-based antagonism
    e. Decrease potency – receptor-based antagonism

Quiz for Session 2-3

1. In order to find out how long a drug will stay in the body and what receptors it binds to, it is sufficient to check:
    a. Pharmacognosy
    b. Pharmacodynamics
    c. Pharmacokinetics
    d. **Pharmacodynamics and Pharmacokinetics**
    e. All three sections: Pharmacognosy, Pharmacodynamics, and Pharmacokinetics
2. Drug potency increases when:
    a. Kd increases – *potency would decrease*
    b. **EC50 decreases**
    c. Emax increases – *involves efficacy*
    d. Emax decreases – *involves efficacy*
    e. Both A and C are correct answers

3. Drug A and Drug B have a similar effect on the body, i.e. result in comparable decreases in the arterial blood pressure. However, the same maximal blood pressure drop is achieved with just 5-mg oral dose of Drug A, but 20-mg oral dose of Drug B. Please identify the statement that is most likely to be true:
    a. Drug A has a 4-times higher efficacy than Drug B
        i. *Same maximal BP drop means same efficacy; Would have been correct if talking about potency*
    b. Drug B has a 4-times higher efficacy than Drug A
    c. **Drug A and Drug B have similar efficacies**
    d. Drug A has a higher affinity for the "blood pressure-lowering receptor" than Drug B
        i. *Question doesn't tell you anything about mechanism of action (nothing about the receptor); Would have been correct as Drug A higher affinity = greater potency*
    e. Drug B has a higher affinity for the "blood pressure-lowering receptor" than Drug A
4. Drug A is considered safer than Drug B if:
    a. Emax of Drug A is smaller than Emax of Drug B – *Emax doesn't indicate safety*
    b. EC50 of Drug A is smaller than EC50 of Drug B – *Potency doesn't indicate safety*
    c. The difference between Kd of the therapeutic effect and Kd of the toxic effect is smaller for Drug A, compared to Drug B – *Smaller difference would mean less safe*
    d. The difference between EC50 and TD50 is smaller for Drug A, compared to Drug B – *EC50 and TD50 are compared as a ratio, not as difference; regardless, it would mean less safe*
    e. **The ratio of EC50 to TD50 is smaller for Drug A, compared to Drug B –** *Note how the ratio is flipped*
5. As a result of adding a non-competitive antagonist of an agonist drug, the agonist's:
    a. **Efficacy decreases, potency remains the same**
        i. *Non-competitive antagonist would decrease efficacy (Emax), and have no effect on potency (EC50)*
    b. Efficacy remains the same, potency decreases
    c. Efficacy remains the same, EC50 increases
    d. Both efficacy and potency decrease, but the effect is stronger on the drug's potency
    e. Non-competitive antagonists do not affect dose-response curves for agonist drugs

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Session 4: Pharmacokinetics I and II (*4 questions*)

Pharmacokinetics – what the body does to the drug

1) Dosage form – solid, liquid, semisolid, inhalations
2) Route of administration
    - Local (for minimal/slow systemic absorption) = topical, deeper tissues
    - Systemic (for absorption into bloodstream, distribution via circulation) = oral, sublingual, inhalation, parenteral
3) Passage across biological membranes
    - Passive Diffusion – Influence of pH
        - Background:
            - Non-electrolytes (unionized) = lipid-soluble = cross readily
            - Strong electrolytes (ionized) = water-soluble = no passive diffusion
            - Most drugs are **weak electrolytes** = ionization is pH-dependent
                - According to the HH equation, when **pH = pKa, the drug is 50% ionized**

pH *increased* by 1 pH = pKa + 1 -> pH = pKa + log (10) Weak **acids** ([A-]/[HA]) = 10; **>90% ionized** = ***impermeable*** Weak **bases** ([B/[BH+]] = 10; **<10% ionized**	pH *decreased* by 1 pH = pKa - 1 -> pH = pKa + log (0.1) Weak **acids** ([A-]/[HA]) = 0.1; **>90% ionized** Weak **bases** ([B/[BH+]] = 0.1; **<10% ionized** = ***impermeable***

    - **Increased ionization = decreased membrane permeability**
        - Weak acids become *impermeable* when pH is *increased*
        - Weak bases become *impermeable* when pH is *decreased*
    - A drug will become **less ionized** (**more lipid-soluble**) at a pH ***similar*** to its own pH
- Partition Coefficient, **LogP**
    - Background:
        - Measure of **lipophilicity** of a drug; important because it impacts processes such as solubility, distribution, ligand recognition, routes of clearance for excretion
    - Partition coefficient (P) = ratio of the concentration of neutral (un-ionized) solute in **lipid/water**
        - P is determined by pKa of the drug and pH of the body fluids
        - **LogP > 0 = lipophilic** (can pass through membranes)
            - *Note*: LogP cannot be *too high* because if a drug is too lipophilic, the drug will not go to solution
            - **Ideal: LogP < 5**
        - LogP = 0 = equally partitioned
        - LogP < 0 = **hydrophilic** (cannot pass through membranes)
- Passage **increases** when:
    - Molecular size decreases
    - Degree of ionization decreases (higher LogP) = increased lipid solubility
    - Concentration gradient increases
    - Tissue inflammation (paracellular spaces widen)
- Effects of pH
    - Acidic drugs (e.g., Aspirin) are largely unionized at gastric pH = absorbed from the stomach
    - Basic drugs (e.g., Codeine) are largely ionized in the stomach = absorbed from the intestine
    - **Ion Trapping**
        - Acidic drugs, largely unionized in the stomach, cross the gastric mucosal membrane
        - They encounter a higher pH in the mucosal cell (pH = 7.0) and plasma (pH = 7.4) and become ionized
        - The drug becomes trapped, which prevents their easy escape
        - This phenomenon may contribute to gastric mucosal cell damage caused by Aspirin
    - Toxicology Application
        - Acidic drugs are ionized at higher pH = alkaline urine
            - They do not diffuse in the kidney tubules and are excreted faster

4) Absorption

- Factors affecting absorption – all routes of administration (*except IV, 100% availability*)
    - Passage across membranes
        - Influence of pH (ionization status)
            - Decreased ionization = increased lipid solubility = increased absorption
        - Influence of concentration:
            - Increased drug concentration = increased concentration gradient = increased absorption

- Aqueous solubility – rate of dissolution of drugs given in solid form
    - For poorly water-soluble drugs (e.g., Aspirin), dissolution (rate at which drug gets to liquid form) controls absorption
- Area of absorbing surface (i.e. intestine)
    - Increased area = increased rate of absorption
- Vascularity of the absorbing surface – important role of the heart
    - Increased blood flow = increased drug removal from the site = increased concentration gradient = increased absorption
    - Diffusion of drugs across capillaries is dependent on the rate of blood flow through them rather than on lipid solubility of the drug or pH of the medium
- Other factors
    - Oral ingestion
        - Food – presence of food delays gastric emptying and dilutes the drug -> retards absorption
        - Degradation by acid and digestive enzymes – certain drugs are degraded in the GI tract (enteric-coated tablets, sustained release preparations)
        - Antibiotics -> altered GI flora -> effect on enterohepatic cycling of oral contraceptives
        - Decreased gut wall motility (e.g., TX w/ anticholinergics, opioids; elderly patients) -> compromised absorption
        - Drug-induced mucosal damage -> altered absorption
    - Parenteral injections
        - Intramuscular and subcutaneous – drugs deposited directly in the vicinity of the capillaries all pass readily; absorption from subcutaneous is *slower* than intramuscular (less vasculature)
            - Heat, massage, and vascular exercise -> vasodilation -> increased blood flow -> increased absorption
            - Vasoconstriction -> decreased blood flow -> decreased absorption
                - E.g., Adrenaline (EPI) with local anesthetics, ice packs, tourniquets
        - Intravenous – drugs injected/infused directly into the bloodstream *bypasses* absorption
            - Most IV drugs should be administered over a period of one minute (blood circulation time through the body = cardiac output) to avoid concentration spikes and allow discontinuance in case of untoward effects
        - Indications:
            - 1) Rapid onset of effect is necessary (emergencies)
            - 2) Oral ingestion is precluded (patient's condition)
            - 3) Oral bioavailability is low

- **First-Pass (Pre-Systemic) Metabolism**
    - 1) Drug administered and absorbed in the gut
    - 2) Drug passes through the mucosa to the interstitial fluid
        - First barrier = enzymes breakdown drug = metabolism before systemic metabolism (*but minor*)
    - 3) Drug absorbed into the portal vein and gets metabolized in the liver before it enters the systemic circulation
        - A **first pass** of high drug concentration through the liver can significantly reduce the quantity of drug reaching the systemic circulation (e.g., opioid analgesics, antibiotics)

    - Characteristics of Drugs with *High* First-Pass Metabolism
        - Oral bioavailability of such drugs is increased in patients:
            - A) With severe liver disease
            - B) Concurrently taking another drug that competes in first-pass metabolism (competition of enzymes)
            - C) With a low rate of hepatic metabolism (genetically-determined)
        - Oral dose of such drugs is substantially higher than sublingual or parenteral dose
- **Bioavailability** (F)
    - Definition: fraction of the administered dose of a drug that reaches the systemic circulation in the **unchanged** form
    - Determined from the exposure (**area under the curve, AUC**) after **oral** (PO) vs. **intravenous** (IV) dose
        - **IV = 100%** bioavailability
        - **Intramuscular** and **subcutaneous < 100%** due to loss at the injection site caused by drug binding
        - **Oral ingestion <100%** due to
            - 1) Incomplete absorption (poor disintegration, low water solubility)
            - 2) First pass metabolism in intestinal wall/liver
- **Bioequivalence**
    - Definition: the absence of a significant difference in the rate and extent to which the active ingredient becomes available when administered at the same molar dose under similar conditions in an appropriately designed study
    - Formulations from different batches/different manufacturers may have the same amount of the drug (= chemically equivalent), but yield different blood levels (= *not biologically equivalent*)
        - Important for drugs with
            - 1) Low safety margins
            - 2) The need for precise dosage control (e.g., oral hypoglycemics, oral anticoagulants)

5) Distribution

- Factors that determine the rate, sequence, and extent of drug distribution
    - Physicochemical properties of the drug
        - **Lipid solubility** (Increased LogP = faster equilibrium with interstitial fluid)
        - **Ionization at physiological pH** (pKa value of the drug)
    - **Fat:Lean Body Mass Ratio** (Increased BMI -> increased accumulation of drug in adipose tissue)
    - **Cardiac output** and **regional blood flow** (the determinant of lipophilic drug uptake rate)
    - **Binding to plasma proteins** and **tissue reservoirs** (affinity for different tissues)
    - **Pathological conditions** (e.g., congestive heart failure, uremia, liver cirrhosis)
        - Altered distribution of body water, membrane permeability, protein levels, accumulation of metabolites that displace the drug from binding sites
- **Volume of Distribution (Vd)**
    - Definition: The hypothetical amount of water by which a particular dose (all the drug in the body) would have to be diluted to produce a given **plasma** concentration, assuming that no drug amount has been lost through incomplete absorption, metabolism, or excretion
        - Useful indicator of how drugs are dispersed among the various body compartments and, together with drug clearance, important pharmacokinetic parameter
    - 1) Drug remains in **intravascular compartment** (drugs extensively bound to plasma proteins)
        - **Vd = volume of plasma (~3L)**
    - 2) Drug evenly distributed in **all** fluid compartments

        - **Vd = volume of body fluids (~41 L)**
    - 3) Drug sequestered in selected **tissue/target** (actively transported against concentration gradient)
        - **Vd >> plasma volume, or even total body fluids (>41 L)**
        - So, high Vd = the drug has accumulated somewhere, and little of it is left in the plasma
- Plasma protein binding
    - Important proteins:
        - **Albumin** – acidic drugs
        - **a1-acid-glycoprotein** – basic/cationic drugs
    - Clinical implications:
        - Plasma drug concentrations refer to bound *and* free drugs -> consider the degree of protein binding
        - High plasma protein binding -> drug largely restricted to vascular compartment (Low Vd)
        - The bound fraction not available for action, but in equilibrium with free drug
        - High plasma protein binding -> drug long acting (the bound fraction not available for metabolism or excretion)
            - Unless the drug is actively taken by organs (plasma protein is a carrier) = increased metabolism
        - **Hypoalbuminemia** -> decreased binding -> increased concentration of free drug
        - **Pregnancy and inflammatory disease** -> increased a1-acid-glycoprotein -> increased drug binding -> decreased concentration of free drug
        - More than one drug can bind to the same site(s) on albumin -> displacement of drug bound with *lower* affinity. Significant for:
            - Highly bound drugs with small Vd (albumin-bound acidic drugs)
            - Administered in large doses
            - Characterized by a narrow margin of safety
            - When metabolism/excretion are decreased
- **Redistribution**
    - Phase I – where the drugs go first
        - **Highly vascularized organs** = heart, kidneys, liver, lungs, brains
    - Phase II – where the drugs got to next with time
        - **Bulk organs** with low perfusion, but high capacity = muscles, skin, fat
        - Can handle more drugs = deposited in high capacity organs
    - Phase III – the re-distribution phenomenon
        - **Saturation** with the drug as a result of subsequent drug injections/infusion
- Saliva
    - Potential applications
        - 1) Therapeutic
            - Systemic administration of drugs to achieve a sustained therapeutic concentration in the saliva for a local effect -> removing the need for intraoral application (e.g., fluoride and antiplaque agents for caries prevention)
        - 2) Diagnostic
            - Measurement of drug levels in the saliva for a non-invasive determination of the free drug concentration in plasma
- Restricted Access
    - **Blood-Brain-Barrier (BBB)**
        - Inflammation of the brain/meninges *increases permeability* of anatomical barriers

        - BBB is *deficient* in the **medulla** (e.g., lipid-insoluble drugs are emetic) and in the **anterior hypothalamus**
    - **Placenta**
        - Highly lipophilic drugs penetrate *easily*, and distribution is dependent on the rate of maternal blood flow through the placenta
            - Even sparingly lipid-soluble drugs accumulate in the fetus if administered to the mother in multiple doses (risks of developmental defects in the embryo and fetus (=teratogenicity)
        - Virtually no water-soluble drug from a single administration may gain access to the fetus

Session 5: Clinical Case Scenario #2 (*1-2 questions*)

1. What is the most likely mechanism of the loss of the analgesic effect of Aspirin?
    a. **Omeprazole (Prilosec)** – proton pump inhibitor
        i. **Increases the pH in the stomach** -> larger fraction of aspirin becomes **ionized** -> drug is being trapped in the stomach and cannot move across the membrane and become absorbed
2. Volume of Distribution of Midazolam (1.0 mg dose) at the end of the first infusion (plasma concentration 200 ng/mL) was:
    a. V = D/Cpo
        i. D = drug quantity administered in a single dose
        ii. Cpo = drug concentration in plasma at time 0
    b. V = (1.0 mg)/(200 ng/mL) = (1.0 mg)/(0.0002 mg/mL) = 5000 mL = **5 L**
    c. *Note*: By the end of the first infusion, most drugs stay *within* the circulation
        i. Normally, plasma volume is about half of total blood volume, so if this was a normal, healthy individual, the total blood volume of this individual would be ~10 L (which doesn't make sense)
            1. Normal healthy individual plasma volume ~3 L (therefore total blood volume ~6 L)
        ii. So, this means that some of the drug has already *left* the circulation
3. Volume of Distribution of Midazolam (1.0 mg dose) right before the next infusion (plasma concentration 20 ng/mL) was:
    a. V = (1.0 mg)/(20 ng/mL) = (1.0 mg)/(0.00002 mg/mL) = 50,000 mL = **50 L**
    b. *Note*: As the volume of distribution gets *larger*, the plasma concentration *decreases*
4. Now let's assume that, after several re-infusions, the dentist did not have to add subsequent doses anymore, and the Midazolam plasma concentration at the steady state was 1.5 ng/mL. What is the apparent Volume of Distribution of Midazolam in this patient?
    a. V = (1.0 mg)/(1.5 ng/mL) = (1.0 mg)/(0.0000015 mg/mL) = 666,666 mL = **667 L**
5. Since Midazolam elimination half-life is approximately 3 hours, why was the dentist repeating the initial (loading) dose every 15 minutes?
    a. **Redistribution** – all tissues that have high fat content needs to be filled (Midazolam is a lipophilic drug)
        i. This is important for all patients (regardless of fat content) – if the patient had less fat, the loading dose would just be different
6. Why did the dentist choose the lower limit of the FDA-recommended loading dose?
    a. **Hepatic impairment (liver cirrhosis)**
        i. Decreased protein synthesis = decreased albumin
            1. Midazolam is ~97% protein bound, so decreased protein (albumin) means an increased free-fraction of the drug (active)

        2. Lower level of protein = higher level of free drug = need to account for initial loading dose
    ii. Advanced liver disease = increased bilirubin content
        1. Competes with other drugs for protein binding sites
    iii. Liver cirrhosis = compromised metabolism = half-life of drug increases
    iv. *Note*: For hydrophilic drugs, lower protein = higher fluid volume = increased volume of distribution
7. In liver disease, the volume of distribution is likely to be:
    a. **Increased**
        i. Liver disease = decreased protein binding = more free-floating drug = more drug leaves the circulation = concentration of drug in plasma is lower and volume of distribution is greater
8. In heart failure, the volume of distribution is likely to be:
    a. **Decreased**
        i. Heart failure = decreased perfusion of organs = decreased distribution of drugs to peripheral tissues
        ii. Heart failure = increased edema = more difficult for drugs to leave circulation
9. In obese patients, the volume of distribution of lipophilic drugs is likely to be:
    a. **Increased**
        i. More fat for the drug to stick to = more drug outside of the circulation

Quiz for Session 4-5

1. Which dosage form can be used to best avoid the first-pass metabolism?
    a. Controlled release tablet – *tablet enters through GI tract (enteric route = first-pass)*
    b. Enteric coated tablet – *tablet enters through GI tract (enteric route = first-pass)*
    c. Soft capsule – *tablet enters through GI tract (enteric route = first-pass)*
    d. **Transdermal patch** – *directly absorbed through the skin*
    e. All of the above because first-pass metabolism is associated only with parenteral injections
2. Aspirin is a weak organic acid with a pKa of 3.5. What percentage of a given dose will be in the lipid-soluble form in the small intestine (pH=6)?
    a. **Less than 1%** - *increase in pH by 1 = weak acids become more ionized by 10-fold = impermeable (water-soluble); in this case, pH is almost 3 times greater so ~1000-fold*
    b. About 10%
    c. About 50% - *this occurs when pH=pKa*
    d. About 90%
    e. More than 99%
3. Which drugs are expected to accumulate in tissues with a low pH?
    a. Strong acidic electrolytes (ionized acids) – *strongly ionized acids or bases won't accumulate anywhere = won't pass through membrane*
    b. Nonelectrolytes (unionized) – *won't accumulate since it will easily pass through membranes*
    c. Weak organic acids – *acidic environments = weak acids become permeable (unionized)*
    d. **Weak organic bases** – *acidic environments = weak bases become ionized, impermeable, and trapped (will accumulate)*
    e. Both A and C are correct answers
4. Distribution of drugs to specific tissues:
    a. Is independent of blood flow – *false; depends on blood flow*
    b. Is independent of the solubility of the drug in that tissue – *false; depends on solubility*
    c. **Depends on the unbound drug concentration gradient between blood and the tissue**

d. Is increased for drugs that are strongly bound to plasma proteins – *false; is decreased for drugs that are bound to plasma proteins*
e. Has no effect on the time it takes to eliminate the drug from the body – *false; increased distribution = increased half-life (time for drug to be eliminated from body)*

5. The patient receives Fentanyl (log P=4.0; Vd = 250L). What intravenous loading dose does he need to rapidly achieve a therapeutic plasma level of 1 ng/mL?
   a. 4 mcg (micrograms)
   b. 4 mg
   c. 250 ng
   d. **0.25 mg**
      i. $Cp_0 = \frac{D}{Vd} \Rightarrow D = Cp_0 \times Vd$
      D = 1 ng/mL x 250 L
      D = 1 µg/L x 250 L
      D = 250 µg = 0.25 mg
   e. 250 ng/mL
6. A drug's amount in the extravascular compartment is 100 times the amount in the plasma. What is the Volume of Distribution in a patient with 8L of blood and 4L of plasma?
   a. 4 L
   b. 8 L
   c. 101 L
   d. **404 L**
      i. $\text{Drug Concentration in Plasma} = \frac{\text{Total Drug Dose}}{\text{Volume of Distribution}}$
      $\frac{\text{Drug Amount in Plasma}}{\text{Volume of Plasma}} = \frac{\text{Total Drug Dose}}{\text{Volume of Distribution}}$
      $\frac{1}{4\text{ L}} = \frac{101}{\text{Volume of Distribution}}$
      $\text{Volume of Distribution} = 4\text{ L} \times 101 / 1$
   e. The data are insufficient to answer this question

Session 6: Pharmacokinetics III and IV (*4 questions*)

Pharmacokinetics – what the body does to the drug

6) Metabolism

- Four Main Processes:
  - Formation of pharmacologically active drug metabolites (Phase I)
    - Observed effect = drug effect + drug metabolite effect
    - *e.g. Morphine, Codeine, Diazepam*
  - Conversion of inactive drugs (Prodrugs) to pharmacologically active metabolites (Phase I&II)
    - *e.g. Acyclovir, Bacamipicillin, Clopidogrel, Levodopa, Methyldopa*
  - Inactivation of drugs and metabolites (Phase II)
    - *e.g. Acetaminophen, Ibuprofen, Lidocaine, Propranolol*
  - Conversion of nonpolar -> polar (lipid-insoluble) for renal/biliary excretion
    - Lipid insolubility prevents reabsorption in renal tubules and bile ducts
    - *Note*: Most water-soluble drugs are *not* biotransformed and are excreted *unchanged*

Phase I	**Phase II**
Non-synthetic (active/inactive metabolites)	**Synthetic** (mostly inactivating)
Oxidation, reduction, hydrolysis	**Conjugation with endogenous groups**
Hemoprotein **Cytochrome P450 (CYP)** isoenzyme families (e.g. **CYP3A4, CYP2D6**)	
Microsomal = inducible by drugs/food	Microsomal = hepatic and non-hepatic = **glucuronide**

Non-Microsomal = not inducible; affected by genetic polymorphisms	Non-Microsomal = cytosol, nucleus = **glutathione** (prevents metabolism-induced drug toxicity)

- Phase II (Synthetic) Reaction: Glucuronide Conjugation
  - Reaction: UDP-Glucuronosyl Transferases (UGTs) transfers glucuronide
    - Ex) Acetaminophen
      - Hydrogen on hydroxyl group replaced by glucuronide
    - Other examples: *Aspirin, Diazepam, Metronidazole, Morphine*
  - Process: **Enterohepatic Cycling**
    - 1) Glucuronidation favors excretion in bile
      - Bile -> GI tract -> Excretion via feces
    - 2) Hydrolysis of drug glucuronides by gut flora
      - Removes glucuronide -> frees drug
    - 3) The released free drug is reabsorbed
      - Implication = **prolonged duration of action**
      - *e.g. Oral Contraceptives*
- Factors Affecting Drug Metabolism
  - 1) **Genetics**
  - 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**
    - Increased binding = decreased metabolism due to less free drug available
      - This includes competition amongst drugs for binding sites
      - *E.g. Sulfonamides, Warfarin, Phenytoin*
    - Increased binding = increased metabolism due to increased delivery of drug to the liver
      - Limited by hepatic blood flow
      - *E.g. Lidocaine*
  - 4) **Enzyme Inhibition**
    - Enzyme availability is limited due to competition between two drugs
      - If metabolized by saturation kinetics -> capacity-limited metabolism
      - E.g. Phenytoin and Warfarin competing for CYP2C9
    - Drug inhibition of enzyme activity
      - Inhibition of drug metabolism occurs in a dose-dependent manner and can precipitate **toxicity**
  - 5) **Microsomal Enzyme Induction** (drugs induce enzymes)
    - Drug interaction with DNA -> increased synthesis of enzyme protein -> increased activity of mixed-function oxidases (CRP) and UGT) -> increased rate of drug metabolism (2-4x)
      - E.g. Phenytoin, Rifampin – several CYP enzymes
    - Consequences of Enzyme Induction
      - Decreased intensity/duration of action of drugs inactivated by metabolism
      - Increased toxicity (increased synthesis of highly reactive intermediaries)
      - Increased pharmacokinetic tolerance (loss of drug responsiveness)
      - Increased metabolism of endogenous chemicals
      - Acute Intermittent Porphyria
- Conditions that can Affect Hepatic Drug Metabolism
  - Decrease
    - **Age**: Neonatal and elderly = less enzymes

        - **Hypothyroidism** = decreased synthesis of metabolic enzymes
        - **Cirrhosis, heart failure** = decreased hepatic blood flow
        - **Stress, inflammation** = decreased free drug delivery
        - **Drug and other factors (e.g. infections)** = reduce hepatic blood flow
    - Increase
        - **Hyperthyroidism** = increased synthesis of metabolic enzymes
        - **Uremia** = decreased albumin binding capacity, increased free drug delivery
        - **Chronic alcohol use** = induction of CYP enzymes

7) Excretion

- Biliary excretion
    - Active transport of free drug and drug metabolites (Phase II, particularly glucuronides)
        - Plasma -> hepatocytes -> bile (-> intestine -> feces)
        - *E.g. Erythromycin, Ampicillin, Rifampin, Tetracycline, Oral Contraceptives*
    - **Enterohepatic Recycling** (due to gut flora) can prolong the duration of drug action
        - Similarly, drugs excreted through saliva are available for reabsorption from the GI tract
        - *E.g. Antibiotics*
- Pulmonary excretion
    - A primary route for the elimination of gases and volatile liquids (e.g., general anesthetics, alcohol), drive 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 be passive diffusion) is ***lipid solubility***
        - Milk pH (7.0) < Plasma pH (7.3-7.4)
        - Weak basic drugs are more concentrated in the milk as it is ionized in a more acidic environment (trapped)
    - *Drugs of particular concern include Lithium, Anticancer Agents, Isoniazid*
- Renal excretion
    - = [Glomerular Filtration] + [Tubular Secretion] – [Tubular Reabsorption]
        - **Glomerular Filtration**
            - Passive
            - Plasma-bound drugs is not filtered; all free drug (lipid soluble or insoluble) is filtered
            - Glomerular filtration of a drug depends on renal blood flow
                - Decreased renal blood flow = decreased GFR = decreased excretion of drug
            - GFR declines progressively after the age of 50
        - **Tubular Reabsorption**
            - Passive
            - **Lipid-soluble** drugs get reabsorbed (along with 99% of filtrate)
            - Lipid-insoluble/highly ionized drugs are not reabsorbed
            - 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
        - **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)
            - Plasma protein-bound drugs cannot be metabolized nor filtered, but it is more easily secreted
    - 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

Kinetics of Elimination

- **Clearance (CL)** = **Rate of Elimination/Plasma Drug Concentration**
    - = ***k x Vd***
- *Most* drugs are eliminated by **first-order kinetics:**
    - A constant ***fraction*** of drug present in the body is eliminated in a unit of time
    - The rate of elimination is directly proportional to drug concentration
    - Clearance remains ***constant*** in 1st order kinetics
- **Zero-Order Kinetics** – when mechanisms of elimination are **saturated**
    - A constant ***amount*** of drug is eliminated in a unit of time
    - The rate of elimination remains ***constant***, independent of drug concentration
    - Important examples: **Aspirin**, Ethanol, Phenytoin; Drug Overdose (Poisoning)
- **Half-life (t1/2)** – the time taken for its plasma concentration to be reduced to one half of its original value
    - According to the graph and the percentage calculations, ***nearly complete drug elimination in 4-5 half-lives***
    - For drugs eliminated by 1st-order kinetics, **t1/2 remains constant**
        - Vd and CL do not change with dose, so t1/2 also does not change with dose; So the drug is eliminated by a fraction
    - For drugs eliminated by zero-order kinetics, t1/2 is ***not constant***
        - **t1/2 increases with dose**
        - **CL progressively decreases as dose is increased** (rate of elimination is the same)
    - Useful in determining:
        - 1) The rate of drug disappearance
        - 2) The concentration of drug remaining after a given period of time
- **Capacity-Limited Metabolism (1st -> Zero-Order Kinetics)**
    - The elimination of some drugs (e.g., Phenytoin, Warfarin) approaches saturation over the therapeutic range
        - The kinetics change from 1st order to Zero-order as the drug dose increases; saturate the system
        - Plasma drug concentration increases disproportionately with increase in dose
    - Includes **Aspirin** and **Ethyl Alcohol**
        - A low dose, aspirin works under first-order kinetics since the system is not yet saturated
        - But, with increased dose, it will switch to zero-order kinetics (system is saturated)
            - Half-life will increase = takes much longer to eliminate the drug
- Assuming 1st-order elimination kinetics and no change in the dosing rate:
    - A constant dose repeated *before* the expiry of 4 half-lives -> increased peak plasma drug concentration
        - **Accumulation** will occur
    - A **plateau (steady-state) average plasma drug concentration (Cpss)** is reached in **4-5 half-lives**, with the assumption that the dose interval is shorter than the half-life; **regardless of dosage**

        - If the dose interval >> t1/2, you will not reach plateau due to input and elimination balance
- Important Formulas:
    - If an immediate pharmacologic effect is needed, a **loading dose (LD)** of the drug must be administered
        - Dependent on Vd and also need to consider F (bioavailability) of the drug
    - **Maintenance dose (MD)** is used to replace the eliminated drug
        - Dependent on CL – tells you how much drug is eliminated
    - For a drug given once every half life, you can assume that the LD is approximately twice the MD

$$Cp = \frac{Dose}{V_d} \qquad Cp_{ss} = \frac{Dose\ Rate}{CL}$$

$$Loading\ Dose = \frac{target\ Cp \times V_d}{F} \qquad Maintenance\ Dose\ Rate = \frac{target\ Cp_{ss} \times CL}{F}$$

$1\ t_{1/2}$ – **50%** drug is eliminated
$2\ t_{1/2}$ – **75%** (50% + 25%) drug is eliminated
$3\ t_{1/2}$ – **87.5%** (50% +25% + 12.5%) drug is eliminated
$4\ t_{1/2}$ – **93.75%** (50% + 25% + 12.5% + 6.25%) drug is eliminated

Session 7: Clinical Case Scenario #3 (*1-2 questions*)

1. What was the rate of Lidocaine infusion?
    a. Dose rate = target Cpss x CL = (3 mg/L)(640 mL/min) = **1.92 mg/min**
2. How long did it take to reach 96.875% of Cpss?
    a. 96.875% = 5 half-lives -> 5 half-lives (1.4 hours) = **7 hr**
3. What potential modifiers of the dosage of lidocaine (lipophilic) should be considered?
    a. **Obesity**
        i. Distribution to tissues where it doesn't act (adipose tissue) -> want to increase dose
        ii. Ratio of lean/fat tissue -> want to decrease dose
    b. **Cimetidine** – inhibit drug metabolism, including lidocaine, by blocking CYP3A4 (enzyme)
        i. CYP3A4 = responsible for metabolizing ~50% of drugs -> want to decrease dose
            1. CYP2D6 = responsible for metabolizing ~25% of drugs
        ii. Also decreases hepatic blood flow (*look below*)
    c. **Propranolol** – decrease hepatic blood flow
        i. Lidocaine undergoes fast metabolism in the liver and is blood flow-limited (how much lidocaine is delivered to the liver) -> want to decrease dose
4. What potential modifiers of the dosage of Tylenol #3 (includes Codeine) should be considered?
    a. **Cimetidine** – inhibit drug metabolism, by blocking CYP2D6 (enzyme)
        i. Codeine = very little analgesic activity, but gets metabolized to morphine by CYP2D6
            1. Codeine = prodrug that needs to be metabolized for therapeutic effect
        ii. Tylenol #3, when given with enzyme inhibitor = decreased analgesic effect -> want to increase dose
        iii. *Note*: CYP2D6 = genetic polymorphisms
5. How much morphine did the other patient inject?
    a. Time of initial dose = 6 hours earlier
        i. If half-life = 3 hours -> 2 half-lives passed (25% remaining)

1. So at 100% = 0.8 mg/L (0.2 mg/L x 4 = 0.8 mg/L)

b. Cp = dose/Vd
    i. (0.8 mg/L)(200 L) = **160 mg**

Quiz for Session 6-7 (+ Practice Questions)

1. Drug metabolism in humans usually results in a product that is:
    a. **Less lipid soluble than the original drug** – *metabolism = eliminate = don't want it to go into tissues = need it to be less lipid soluble (impermeable)*
    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. Hepatic enzyme induction typically leads to the following change: (*enzyme induction = increased activity of enzyme)*
    a. Conversion to non-polar (lipid-soluble) inactive metabolites – *false; increased enzyme activity would increase conversion to polar metabolites (lipid insoluble) metabolism for elimination*
    b. Formation of Prodrugs – *false; enzyme induction would increase activity of prodrugs (converted to active metabolites), but not the actual formation of prodrugs*
    c. Shrinking of smooth endoplasmic reticulum – *false; enzyme induction associated with protein synthesis, so this would increase smooth ER*
    d. An increase in drug's Log P – *false; higher logP = more lipophilic = more permeable (opposite effect of enzyme induction)*
    e. **A decrease in the duration of drug action** – *increase enzyme activity = increase metabolism to the inactive form = decrease duration of action*
3. Which single variable will allow you to determine how long it will take to reach a steady-state level for an IV infusion of a drug cleared by first-order kinetics?
    a. Bioavailability
    b. Dosage rate (mg/hr)
    c. **Elimination half-life**
    d. Infusion rate
    e. Volume of distribution
4. A prodrug requires first-pass metabolism by hepatic CYP1A2. This patient's liver status (HepC) would likely have the following effect(s) on therapy with the prodrug:
    a. An increased rate of drug metabolism
    b. **Less than normal therapeutic response to drug therapy** – *Damaged liver = drug cannot be converted to active metabolite form*
    c. Increased sensitivity to drug therapy
    d. A lower oral dosage should be used
    e. Both C and D are correct answers
5. A patient's blood sample shows a drug level of 4 ug/mL. The drug's half-life is 25 days. If you discontinue the medication, how long will you have to wait for the drug level to fall to 1 ug/mL?
    a. 25 days
    b. **50 days**
    c. 75 days
    d. 82.5 days
    e. 100 days
6. Infusion of Procainamide ($t_{1/2}$ = 2 hours) begins at 9:00AM and blood taken at 1:00PM shows Cp = 3 mg/L. What is the steady-state Cp after 16 hours?
    a. 3 mg/L

b. **4 mg/L**
c. 6 mg/L
d. 9.9 mg/L
e. 15 mg/L
f. *How to solve*:
    i. 9:00AM – 1:00PM = 4 hours; 4 hours = 2 $t_{1/2}$
        1. After 2 half-lives = 75% of steady-state (50% = 1, 75% = 2, 87,5% = 3, etc)
        2. 75% of steady-state Cp = 2 half-lives = 3 mg/L
            a. 100% = steady-state Cp
        3. So, steady-state Cp = 3 mg/L x 100% / 75% = **4 mg/L**

7. Gentamicin (CL by glomerular filtration) is given at 100 mg 3 times a day. If creatinine CL is one third of normal, the modified dosage should be:
    a. 20 mg 3 times a day
    b. **33 mg 3 times a day** – *Need to be applied in same interval, but need to change the dose since 1/3 of the dose is cleared (volume of plasma) because of compromised kidney function*
    c. 100 mg 2 times a day
    d. 100 mg 3 times a day
    e. 300 mg 3 times a day
8. A decreased hepatic blood flow usually leads to an increased drug action EXCEPT:
    a. **Prodrugs metabolized by the liver**
    b. Drugs with high first pass metabolism in the intestinal wall
    c. Drugs with high first pass metabolism in the liver
    d. Drugs converted to inactive metabolites by the liver
    e. Both A and B are correct answers

Session 8: Drug Action Modifiers, Adverse Drug Reactions, Pharmacogenetics (*4 questions*)

Drug Action Modifiers

- The common causes of variation among individuals in response to the same dose of a drug:
    - **Pharmacokinetic differences**: varying drug concentrations in the plasma/target site
    - **Pharmacodynamic differences**: number/site of receptors and signal transduction components
    - **Secondary factors**: e.g., patient non-compliance, neurogenic/hormonal tone, etc.

Body Weight and Composition: Vd dependent on body mass; obese vs. muscular

- **Morbid Obesity**
    - Increased fat -> increased redistribution away from target organs -> increase dose
    - Decreased fraction of lean weight -> increased drug/lean tissue (active) -> decrease dose

Age

- **Children (>6 mo.)** often require larger drug doses (per body weight)
    - Increased elimination rates -> drug dose adjustment on the basis of body surface area
    - *Note*: **Neonates (<6 mo.)** = hyper-sensitivity to drugs due to immature hepatic and renal systems
        - + Bilirubin leads to increased amount of free drug
        - + Immature blood/brain barrier
- **Geriatric patients** show changes in responsiveness to drugs: hyper- or hypo-reactivity
    - Decreased renal and hepatic function -> use lower drug doses
        - *Except* prodrugs that need to be metabolized in the liver for proper therapeutic effect -> use higher drug doses

    - Decreased plasma albumin -> decreased plasma protein binding of drugs -> increased free drug
    - Decreased motility and blood flow to intestines -> slower drug absorption
    - Changes in receptor responsiveness (e.g., decreased sensitivity of beta-adrenergic)

Sex and Pregnancy

- **Females**
    - Increased susceptibility to drug interactions by systemic contraceptives
    - Increased risk of drug-induced cardiac arrhythmias
- **Pregnancy**
    - Increased drug metabolism
    - Increased renal excretion (increased cardiac output and GFR), (opposite of geriatric patients)
        - Want to increase drug dose since it's eliminated faster
    - Decreased binding to albumin (similar to geriatric patients)

Race: Differences in EC50 of drugs (e.g., increased EC50 of atropine and beta-blockers in blacks)

Genetics: Drug metabolizing enzyme isoforms; SNPs in structure of enzymes/receptors

Pathological and Psychological States

- **GI Diseases**
    - Decreased absorption of orally-administered drugs (e.g., achlorhydria, diarrhea, celiac disease)
- **Liver Dysfunction (specific hepatic disease, infection, reduced blood flow to the liver)**
    - Decreased hepatocellular function -> increased bioavailability of drugs with high first-pass metabolism
    - Decreased serum albumin -> decreased protein binding of drugs -> increased drug in free form -> decrease dose
    - Decreased drug metabolism and elimination -> increased plasma drug concentration and increased duration of drug action (increased drug half-life) -> decrease dose
    - Prodrugs with hepatic metabolism for activation may become less effective
    - Decreased biliary excretion of drugs (enterohepatic cycling)
    - Insidious effects of drugs that are potentially toxic to their primary organs of elimination
        - E.g., Acetaminophen accumulation -> hepatic necrosis -> further impairment of drug metabolism
- **Kidney Disease**
    - Decreased clearance of drugs that are primarily excreted unchanged -> increased drug half-life -> increased dosage interval
    - Decreased serum albumin -> decreased protein binding of acidic drugs -> increased drug in free form
    - Decreased excretion of inactive metabolites -> increased risk of untoward reactions
    - Renal failure -> increased permeability of blood-brain barrier -> increased effectiveness of centrally-acting drugs (e.g., opiates, barbiturates, benzodiazepines)
        - Decreased GFR -> loop and thiazide diuretics ineffective
- **Congestive Heart Failure**
    - Mucosal edema, vasoconstriction -> decreased drug absorption from the GI tract
    - Decreased perfusion -> decreased Vd/increased plasma drug concentration (but increased Vd for some drugs due to increased extracellular fluid) -> decrease dose
    - Decreased liver perfusion, GFR (increased tubular reabsorption) -> decreased drug elimination -> increased plasma concentration, drug half-life -> decrease dose
- **Thyroid Disease** (non-pharmacokinetic effects)
    - Hypothyroidism -> increased sensitivity to CNS depressants
    - Hyperthyroidism -> increased systemic effects of EPI, decreased potency of morphine
- **Anxiety**: increased requirement for general anesthetics

Drug Factors

- **Variables in drug administration** – *the only factors that are totally under the control of the clinician*
    - Dose, drug formulation, route of administration
    - Timing of administration
        - Avoidance of disturbing side effects if a sedative agent can be given shortly before sleep
            - E.g., The vestibular component of nausea associated with opioid analgesics (minimize nausea)
        - Scheduling of doses with (decreased gastrointestinal upset) or between (increased absorption) meals
- **Drug tolerance** – a state of decreased responsiveness -> increase drug dose to produce a given response
    - **Natural**: Individual is inherently less sensitive to the drug (e.g., blacks are tolerant to mydriatics)
    - **Acquired**: Loss of therapeutic efficacy after prolonged/intensive use of a drug
        - **Pharmacokinetic**: The effective drug concentration is diminished (e.g., metabolic enzyme induction)
        - **Pharmacodynamic**: The reaction to a given drug concentration is reduced (e.g., decreased receptors)
        - **Immune**: Antibodies bind to the drug
    - **Cross-Tolerance**: The development of tolerance to pharmacologically related drugs
        - E.g., Alcoholics are tolerant to barbiturates and general anesthetics
    - **Tachyphylaxis**: Rapid development of tolerance when doses of a drug are repeated quickly

Drug Interactions: Most Dangerous Drug Combinations: (*discussed in later lectures in more detail*)

- **Epinephrine in LA** with
    - **Propranolol** (non-selective beta-adrenergic antagonist)
- **NSAIDs** with
    - **Diuretics** and **Renin-Angiotensin-Aldosterone System Inhibitors** (triple therapy)
    - **Lithium** (mood stabilizer – bipolar disorder)
- **Warfarin** (anticoagulant) with
    - **Non-steroidal anti-inflammatory drugs (NSAIDs)**
    - **Metronidazole** and **Fluconazole**
    - **Sulfonamides, Macrolide**, and **Quinolone antibiotics**

ADE Categories:

- **Side effects**
    - Predicted from the pharmacological profile of a drug, occur at therapeutic doses and reduction in dose usually ameliorates the symptoms (**dose-dependent**)
    - May be based on the same action as the therapeutic effect
        - E.g., Xerostomia by Atropine
        - E.g., Gastric mucosal damage by **NSAIDs**
        - E.g., Cardiac depression by **Lidocaine**
    - May also be based on a different facet of action
        - E.g., Sedative effect of Promethazine, unrelated to its anti-allergic action
    - An effect may be therapeutic in another context
        - E.g., Xerostomia induced by Atropine in control of salivation,
        - E.g., Constipation by Codeine in traveler's diarrhea
- **Toxicity/Poisoning/Extension Effects**
    - Excessive pharmacological action of the drug due to over-dosage or prolonged use
        - Absolute over-dosage: accidental, homicidal, suicidal (analgesics, antidepressants, alcohol)

        - Relative over-dosage: usual dose, but decreased elimination (e.g., renal failure)
    - May result from extension of the therapeutic effect (exaggerated effect)
        - E.g., **Insulin** – hypoglycemia
        - E.g., **Warfarin, Heparin** – spontaneous bleeding
        - E.g., **Furosemide** – hypovolemia
- **Drug Allergy**
    - Immunologically-mediated reaction producing stereotype symptoms (similar to food/protein allergy, allergic diseases) which are unrelated to pharmacodynamic effects of the drug
    - Allergic reactions can occur with very small doses (**dose-independent**)
    - Allergic reactions cannot be produced in non-sensitive individuals at any dose
    - Prior sensitization is necessary; a latent period (>1-2 weeks) after the first exposure (need to develop antibodies)
    - Drugs of importance to dentistry and commonly implicated in allergic reactions:
        - **Penicillins, Sulfonamides, Cephalosporins, Tetracyclines, LAs, Salicylates**
- **Teratogenicity**
    - The capacity of a drug to cause fetal abnormalities when administered to the pregnant woman
    - No drug can be declared to be absolutely safe during pregnancy – all drugs should be avoided unless there are compelling reasons for their use
    - In contrast to adults, drug effects on embryo are often irreversible
        - *Failure of pregnancy* (0-20 days)
        - *Deformities* (21 days-the end of the First Trimester = the most vulnerable period = Organogenesis)
            - Emergency dental treatment only = avoid **Benzodiazepine** sedatives = known human teratogens
        - *Developmental and functional abnormalities* (56 days-)
            - Discolored/deformed teeth and retarded bone growth by **Tetracyclines**
            - Cleft lip/palate by **Phenytoin** and **anticancer drugs (Methotrexate)**
            - Premature closure of ductus arteriosus by **NSAIDs**

Genetic Influences on Drug Metabolism

- Three drug oxidation polymorphisms receiving most clinical attention (including dentistry):
    - CYP**2D6** – affects 25% of all currently used drugs (the most important one = CYP**3A4**)
        - Poor metabolizer CYP2D6 phenotype (7-10% Caucasians, 30% Chinese)
            - Types:
                - 1) Gene deletion -> absence of protein
                - 2) Defective splicing -> inactive enzyme
                - 3) Missense SNPs -> decreased enzyme stability or substrate affinity
            - Consequences:
                - Higher concentrations of parent drug following administration -> greater adverse effects
                - Therapeutic failure of [prodrugs]/[less active forms] requiring CYP2D6 for activation (e.g., Codeine -> Morphine)
        - **Ultra-rapid CYP2D6 phenotype** (30% Egyptians)
            - Type: 1) Gene duplication -> increased active enzyme
            - Consequence:
                - Ultra-rapid conversion to more active drug forms -> increased risk of life-threatening drug effects (e.g., **Codeine -> Morphine**)
    - CYP**2CP** – catalyzes the oxidation of **Warfarin** (anticoagulants; VitK antagonist)

        - Allelic variants of *CYP2C9* encode enzymes with reduced or altered affinities -> up to 90% reduction in Warfarin clearance -> bleeding complications
            - Reduced metabolism of Warfarin = increased drug activity
    - CYP**2C19 –** catalyzes the oxidation of **Clopidogrel** (anti-platelet)
        - Patients with poor or intermediate CYP2C19 phenotypes -> inadequate therapeutic effects (won't be converted to active form)
- **B-Adrenergic Receptor Polymorphisms** – critical sympathetic responses in the cardiovascular, respiratory, and gastrointestinal systems
    - B2-adrenergic receptor genotype variation – affects therapeutic response to selective B2-adrenergic agonists (e.g., Albuterol)
    - Polymorphisms of B-adrenergic receptors and treatment of CV diseases
        - 1) Alteration of agonist or antagonist efficacy (a variant B1 or B2 receptor)
        - 2) Alteration of drug efficacy secondary to an effect of the polymorphism on CV function (indirect effect)
            - E.g., A patient with B2 receptor variant that results in lower systemic vascular resistance -> altered sensitivity to vasodilation via another mechanism, secondary to the altered vascular tone
- Genetic polymorphisms in **dopaminergic** and **antipsychotic drug receptor targets**
    - Drug abuse liability, the reinforcing effects of alcohol, cocaine, and nicotine
    - Incidence of tardive dyskinesias following long-term treatment of Schizophrenia
    - Lack of effectiveness of antipsychotic drugs in some patients with Schizophrenia (dopaminergic, adrenergic, serotonergic and/or histaminergic receptor polymorphisms)

Inherited Diseases that Predispose to Drug Toxicity Relevant to Dentistry

- **Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency**
    - Catalyzes the formation of reduced NADPH, which maintains glutathione in its reduced form
    - Located on X-chromosome (sex-linked)
    - G6PD deficiency common (Mediterranean peoples, African and Indian descent, in East Asia)
    - **Methemoglobinemia** and **hemolysis**
        - Drugs: **Analgesics (Aspirin), Antibacterials (Cirprofloxacin)**
- **Ryanodine R1 Receptor (Ry1R) Variant**
    - Controls intracellular calcium flux from the sarcolemma
    - **Malignant Hyperthermia** and **Muscle Spasm**
        - Drugs: **General Anesthetics – inhalation anesthetics (isoflurane)**

Session 9: Clinical Case Scenario #4 (*1-2 questions)*

1. The patient's condition was likely precipitated by:
    a. Oral examination
    b. LA – *LA wouldn't precipitate an event 4 days later*
    c. Epinephrine – *LA wouldn't precipitate an event 4 days later*
    d. Extraction
    e. **Post-surgical analgesia with Tylenol/Codeine #3** – *Occured 4 days after the procedure*
    f. Psychological stress associated with the procedure
    g. The advanced age of the patient
    h. An unrelated condition of the patient
2. In a short phrase: What is the mechanism of the patient's emergency?
    a. **Ultrarapid CYP2D6** – CNS depression (low BP, respiration) mediated by morphine overdose
3. In a short phrase: How should the patient be treated in the ICU besides the assisted ventilation?
    a. Block morphine receptor (mu-opioid receptor) = **Naloxone**

4. Would there be a need for a modification to a standard treatment protocol for the patient's son?
    a. **Yes**
5. In a short phrase: Please explain why the doctor prescribed a combination medication for pain control.
    a. Extraction = inflammation + acute activation of nociceptive endings
        i. Opioids = relieve non-inflammatory component of the pain

Quiz for Session 8-9 (+ Practice Questions)

1. A decreased hepatic blood flow usually leads to an increased drug action EXCEPT:
    a. **Prodrugs metabolized by the liver**
    b. Drugs with high first pass metabolism in the intestinal wall
    c. Drugs with high first pass metabolism in the liver
    d. Drugs converted to inactive metabolites by the liver
    e. Both A and B are correct answers
2. A decrease in responsiveness to a drug caused by metabolic enzyme induction after prolonged use of a drug is an example of:
    a. Natural Tolerance
    b. Acquired Pharmacodynamic Tolerance – *Decreased number of receptors (what the drug does to the body); this would be an increased/decreased number of receptors*
    c. **Acquired Pharmacokinetic Tolerance** – *What the body does to the drug = metabolism (enzyme induction)*
    d. Cross-Tolerance
    e. Tachyphlyaxis
3. Which adverse reaction is most likely to be genetically-determined?
    a. Allergic reactions – *requires previous exposure (drug dose-independent)*
    b. Extension effects – *extension of normal reaction upon increasing dose (toxicity/overdose)*
    c. Iatrogenic effects – *caused by the doctor*
    d. **Idiosyncrasies**
    e. Teratogenic effects – *effect of drug on fetus*
4. Inhalation anesthesia with Isoflurane might lead to malignant hyperthermia if the patient carries a mutation in the gene encoding:
    a. CYP2D6 – *Not related to hyperthermia; gene associated with codeine-morphine metabolism*
    b. **Ryanodine Receptor 1**
    c. Dopaminergic receptor – *associated with drug abuse/development of addiction*
    d. Beta-1-adrenergic receptor
    e. Glucose-6-phosphate dehydrogenase (G6PD) – *methemoglobinemia/hemolysis*
5. The "ultrarapid metabolizer" phenotype is most likely to be a result of:
    a. Gene deletion
    b. Defective splicing
    c. Missense SNPs
    d. **Gene duplication**
    e. A, B, and C are correct answers
6. A lipophilic drug (F 20%, first-pass hepatic) is inactivated in the liver and excreted through bile and kidney. Cp of active drug will be INCREASED in the following conditions, EXCEPT:
    a. An advanced age – *Associated with compromised liver function*
    b. **Conditions resulting in Pharmacokinetic Tolerance** – *Pharmacokinetic tolerance caused by enzyme induction; would result in faster clearance/removal of the drug = decreased level of active drug*
    c. Congestive heart failure – *Liver-related as CHF decreases blood flow through liver*
    d. Liver disease – *Similar concept*

e. Obstruction of bile ducts – *Drug excreted through bile, so obstruction of bile ducts would compromise excretion*
f. *How to solve:*
    i. *Expect higher levels of the drug if liver is not working*

7. Please identify the typical effect of CHF on drug pharmacokinetics:
    a. Increased absorption from the GI tract - *CHF = edema = decreased blood flow through intestines = decreased absorption*
    b. Increased volume of distribution of lipophilic drugs – *Decreased distribution since blood isn't effectively flowing, and therefore delivered, to tissues*
    c. Increased hepatic metabolism – *Blood flow compromised = decreased metabolism*
    d. Increased renal excretion of ionized drugs – *Blood flow compromised = decreased excretion*
    e. **Increased elimination half-life** – *CHF = edema = decreased blood flow = decreased metabolism = longer half-life of drug*
8. A man with poor CYP2C19 phenotype and acute cardiac ischemia. Which of the following drugs may cause unexpected results?
    a. **Clopidogrel**
    b. Codeine – *2D6*
    c. Warfarin – *2C9*
    d. Isoflurane
    e. Ethanol
9. A child is in coma with cyanosis. She was given codeine with acetaminophen. The child became unresponsive and "turned blue." Which allele might be responsible?
    a. **CYP2D6*1x3** – *2D6 converts codeine to morphine; ultra-rapid metabolism*
    b. CYP2C19*2
    c. CYP2C9*3
    d. UGT1A1*28
    e. DYPD*2A

Midterm Quiz:

1. Please identify the type of information about Ibuprofen (Advil) that you would find in the PHARMACODYNAMICS section of the drug data.
    a. **… competitively inhibits both COX1 and COX2**
    b. … highly protein-bound (more than 99% at 20 mcg/mL)
    c. … metabolized via hepatic oxidation by CYP2C9 to inactive metabolites
    d. … Vd of approximately 0.12 L/kg
2. Drug A and Drug B have the same maximal efficacy in relieving dental inflammatory pain. However, Drug A has the therapeutic index of 40 and ED50 = 600 mg, whereas Drug B has the therapeutic index of 10 and ED50 = 200 mg. Please identify the correct statement.
    a. Drug A should not be used to treat patients
    b. Drug A should be used with caution, whereas Drug B would be a much safer choice
    c. Drug A is expected to be more effective in relieving dental pain than Drug B
    d. **Drug A has a lower potency than Drug B**
3. Relative to Morphine (a full agonist of mu-opioid receptors), Tramadol (a partial agonist) is expected to have a:
    a. **Similar affinity for the opioid-binding site of the mu-opioid receptor, but lower efficacy**
    b. Higher affinity for the opioid-binding site of the mu-opioid receptor, but lower efficacy
    c. Similar affinity for the opioid-binding site of the mu-opioid receptor, and similar efficacy

d. Lower affinity for the opioid-binding site of the mu-opioid receptor, but similar efficacy

4. The action of Pilocarpine, a muscarinic receptor agonist, leading to a decreased efficacy of Albuterol, a beta-2-adrenergic agonist, is an example of:
    a. Receptor-based synergism
    b. Receptor-based antagonism
    c. Functional (physiological) synergism
    d. **Functional (physiological) antagonism**
5. Labetalol, a competitive antagonist of alpha-1-adrenergic receptors, is expected to have the following effect on Epinephrine applied with a local anesthetic and acting on alpha-1-adrenergic receptors:
    a. Increase affinity for the receptors
    b. **Increase EC50**
    c. Increase potency
    d. Decrease efficacy (Emax)
6. A non-competitive antagonist of a receptor is expected to:
    a. Decrease affinity of agonist for the same receptor
    b. Increase affinity of agonist for the same receptor
    c. **Decrease efficacy of agonist acting on the same receptor**
    d. Increase potency of agonist acting on the same receptor
7. The phenomenon of Pharmacodynamic Tolerance is likely to:
    a. Decrease EC50 of the drug
    b. Increase potency of the drug
    c. Increase the intrinsic activity of the drug
    d. **Decrease the drug receptor density**
8. When treating a 5-year-old girl with a middle ear infection, the antibiotic dosage formulation most acceptable to her would likely be:
    a. Tablet
    b. Capsule
    c. Oral suspension
    d. IM injection
9. Please identify the fraction of Aspirin (a weak organic acid, pKa=3.5) that would be readily absorbable in the stomach at the pH of 3.5.
    a. Less than 10%
    b. About 25%
    c. **About 50%**
    d. About 75%
10. Oral bioavailability of a weak base (pKa=8.0) that undergoes first-pass metabolism in the intestinal wall will be increased when:
    a. pH in the intestine is lowered to 5.5
    b. **The drug is administered together with a drug undergoing the same type of first-pass metabolism**
    c. The drug is administered together with a drug undergoing hepatic first-pass metabolism
    d. The patient has recently had a widespread myocardial infarction of the left ventricular wall
11. Patient with 5.5 L of blood and 3 L of plasma receives a drug that is 50% bound to plasma proteins whereas the remaining 50% are distributed outside of the vascular compartment. Volume of Distribution (Vd) of the drug is:
    a. 3 L
    b. 5.5 L
    c. **6 L**
    d. 11 L

12. Patient receives an oral antibiotic in the dose of 500 mg. The oral bioavailability of the antibiotic is 10%. The resulting plasma concentration of the antibiotic is 5 mg/L, and the plasma volume of this patient is 2.5 L. The apparent Volume of Distribution (Vd) of this antibiotic is:
    a. 20 mg/L
    b. 2.5 L
    c. **10 L**
    d. 100 L
13. A drug with LogP=5 and 60% binding to plasma proteins is likely to have its Volume of Distribution DECREASED in:
    a. **Congestive heart failure**
    b. Liver cirrhosis
    c. Obese patients
    d. Patients chronically treated with Warfarin (99% plasma protein bound)
14. Which of the following cytochrome isoforms is responsible for metabolizing the largest number of drugs?
    a. CYP1A2
    b. CYP2C9
    c. CYP2C19
    d. **CYP3A4**
15. Drugs inactivated by hepatic metabolism are likely to show INCREASED toxicity when:
    a. Hepatic blood flow is increased
    b. Enzymes metabolizing these drugs are induced by other drugs
    c. Drug binding to plasma proteins is increased
    d. **Applied with other drugs metabolized by the same mechanism**
16. Enterohepatic cycling:
    a. Facilitates drug excretion
    b. Is compromised by cholecystectomy (gall bladder removal)
    c. **Prolongs drug action**
    d. Results in unwanted pregnancies in patients using oral contraceptives
17. A highly water-soluble drug is excreted unchanged by the kidneys. Please identify the condition that is likely to increase the drug's clearance.
    a. Congestive heart failure
    b. Kidney failure
    c. Liver cirrhosis
    d. **Pregnancy**
18. To correct a life-threatening cardiac arrhythmia, the patient receives an intravenous infusion of Lidocaine (Vd 77L; Clearance 640 mL/min; Half-life 1.4 h) and the target steady-state plasma concentration of the drug is 3 mg/L. The infusion was started at 2:00 PM. What time would you need to collect a blood sample in order to see the Lidocaine plasma concentration of 2.25 mg/L?
    a. 3:40 PM
    b. **4:48 PM**
    c. 5:20 PM
    d. In order to answer this question, it is necessary to know the dose of Lidocaine infused per unit of time (e.g., mg/h)
19. A patient ingests one 100-mg capsule of an anti-arrhythmic drug daily. The drug's oral bioavailability is 10%, elimination half-life 8 hours, clearance 10 L/day, and the steady-state plasma concentration 1 mg/L. If the patient discontinues the medication, how long will it take for the drug concentration to fall to 0.25 mg/L?
    a. 2 hours

b. 8 hours
c. **16 hours**
d. 32 hours

20. The phenomenon of Pharmacokinetic Tolerance is likely to be evoked by:
    a. Drugs that inhibit hepatic first-pass metabolism
    b. Drugs that inhibit hepatic CYP450 enzymes
    c. **Drugs that induce hepatic metabolism**
    d. Antibody binding to the drug
21. An advanced age of the patient is likely to be associated with:
    a. Enhanced drug absorption due to increased intestinal wall motility
    b. Increased drug metabolism due to upregulation of hepatic CYP450 enzymes
    c. **Decreased plasma protein binding of drugs**
    d. Decreased elimination half-life of drugs
22. A drug adverse reaction that occurs at therapeutic doses and can be avoided or diminished by reducing the drug dose is an example of:
    a. Allergy
    b. Idiosyncrasy
    c. **Side effect**
    d. Toxicity
23. Please identify the correct statement about Clopidogrel (an antiplatelet agent activated by hepatic metabolism)
    a. Its dose may need to be reduced in patients with advanced liver cirrhosis
    b. Its dose may need to be reduced in patients carrying CYP2C9 point mutation
    c. **Its potency is likely to be decreased in patients treated with Propranolol, which decreases hepatic blood flow**
    d. Its potency is likely to be increased in patients with CHF
24. A patient's genome includes a SNP associated with an increased risk of hemolysis. A gene polymorphism of which of the following proteins is the most likely culprit?
    a. CYP2D6
    b. CYP2C19
    c. CYP2C9
    d. **Glucose-6-phosphate dehydrogenase (G6PD)**
25. Analgesia with Codeine may lead to opioid overdose (intoxication with morphine) if the patient carries a mutation in the gene encoding:
    a. CYP2C9
    b. CYP2C19
    c. **CYP2D6**
    d. CYP3A4