Pharmacokinetics

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Overview

- Pharmacokinetics examines the movement of a drug over time throughout the body.
- 4 Fundamental Pathways:
  - 1. Drug absorption from the site of administration (input) permits entry of the therapeutic agent (either directly or indirectly) into plasma.
  - 2. The drug may then reversibly leave the bloodstream and distribute into the interstitial and intracellular fluids (distribution.
  - 3. The drug may be metabolized by the liver, kidney, or other tissues.
  - 4. The drug and its metabolites are eliminated from the body (output) in urine, bile, or feces.

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Routes of Drug Administration

- Primarily: Properties of the drug (for ex: water or lipid solubility, ionization, etc.)
- The therapeutic objectives (for ex: the desirability of a rapid onset of action or the need for long-term administration or restriction to a local site).
- Two major routes of drug administration:
  - Enteral
  - Parenteral

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Enteral

- 1. Oral
- 2. Sublingual
- 3. Rectal

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Parenteral

- 1. Intravascular
- 2. Intramuscular (IM)
- 3. Subcutaneous (SC)

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- 1. Inhalation
- 2. Intranasal
- 3. Intrathecal/Intraventricular
- 4. Topical
- 5. Transdermal

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Absorption of Drugs

- Absorption: the transfer of a drug from its site of administration to the bloodstream. The rate and efficiency of absorption depend on the rout of administration. For IV delivery, absorption is complete. Drug delivery by other routes may result in only partial absorption and, thus, lower bioavailability.

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Transport of a Drug from the GI Tract

- 1. Passive diffusion
- 2. Active transport

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Effect of pH on Drug Absorption

- Most drugs are either weak acids or weak bases. Acidic drugs (HA) release a H+ causing anion (A-) to form [2]
- Weak bases (BH+) can also release a H+. However, the protonated form of basic drugs is usually charged, and loss of a proton produces the uncharged base (B).
  - 1. Passage of an uncharged drug through a membrane.
  - 2. Determination of how much drug will be found on either side of a membrane.

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- $pH = pK_a + \log[\text{nonprotonated species}]/[\text{protonated species}]$
  - For Acids: $pH = pK_a + \log [A^-]/[HA]$
  - For Bases: $pH = pK_a + \log [B]/[BH^+]$

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Physical Factors Influencing Absorption

- 1. Blood flow to the absorption site.
- 2. Total surface area available for absorption.
- 3. Contact time at the absorption surface.

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Bioavailability

- Bioavailability is the fraction of administered drug that reaches the systemic circulation. Bioavailability is expressed as the fraction of administered drug that gains access to the systemic circulation in a chemically unchanged form. For example: If 100mg of a drug is administered orally and 70mg of this drug is absorbed unchanged, the bioavailability is seventy percent.

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Drug Distribution

- Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the interstitium (extracellular fluid) and/or the cells of the tissues. The delivery of a drug from the plasma to the interstitium primarily depends on (1)blood flow, (2) capillary permeability, (3) the degree of binding of the drug to plasma and tissue proteins, and (4) the relative hydrophobicity of the drug.

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Blood Flow

- The rate of blood flow to the tissue capillaries varies widely as a result of the unequal distribution of cardiac output to the various organs.

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Capillary Permeability

- Capillary Structure: Capillary structure varies widely in terms of fraction of the basement membrane that is exposed by slit junctions between endothelial cells.
- Blood-drain barrier: To enter the brain, drugs must pass through the endothelial cells of the capillaries of the CNS or be actively transported.

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- Drug Structure: The chemical nature of the drug strongly influences its ability to cross cell membranes. Hydrophobic drugs, which have a uniform distribution of electrons and no net charge, readily more across most biological membranes. These drugs can dissolve in the lipid membranes and, therefore, permeate the entire cell's surface. The major factor influencing the hydrophobic drugs distribution is the blood flow to the area. By contrast, hydrophilic drugs which have wither a nonuniform distribution of electrons or a positive or negative charge, do not readily penetrate cell membranes and must go through the slit junctions.

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Binding of Drugs to Proteins

- Reversible binding to plasma proteins sequesters drugs in a non-diffusable form, and slows their transfer out of the vascular compartment.
- Plasma albumin is the major drug-binding protein, and may act as a drug reservoir.

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Volume of Distribution

- A hypothetical volume of fluid into which a drug is disseminated.

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Water Compartments in the Body

- Once a drug enters the body, from whatever route of administration, it has the potential to distribute into any one of the three.
  - Plasma Compartment: If a drug has a very large molecular weight or binds extensively to plasma proteins, it is too large to move out through the endothelial slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment. As a consequence, the drug distributes in a volume (the plasma) that is about 6% of the body weight or, in a 70kg individual, about 4L of body fluid. Heparin shows this type of distribution.

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- Extracellular fluid: If a drug has a low molecular weight but is hydrophilic, it can move through the endothelial slit junctions of capillaries into the interstitial fluid. However, hydrophilic drugs cannot move across the membranes of cells to enter the water phase inside the cell. Therefore, these drugs distribute into a volume that is the sum of the plasma water and the interstitial fluid, which together constitute the extracellular fluid. This is about 20% of the body weight, or about 14L in a 70kg individual. Aminoglycoside antibiotics show this type of distribution.

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- Total Body Water: If a drug has a low molecular weight and is hydrophobic, it not only can move into the interstitium through the slit junctions, but can also move through the cell membranes into the intracellular fluid. The drug therefore distributes into a volume of about 60% of body weight, or about 42L in a 70kg individual. Ethanol exhibits this apparent volume of distribution.

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Binding of Drugs to Plasma Proteins

- Drug molecules may bind to plasma proteins (usually albumin). Bound drugs are pharmacologically inactive; only the free, unbound drug can act on target sites in the tissues.

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Binding Capacity of Albumin

- The binding of drugs to albumin is reversible.
- Albumin has the strongest affinity for anionic drugs (weak acids) and hydrophobic drugs. Most hydrophilic drugs and neutral drugs do not bind to albumin.

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Drug Metabolism

- Drugs are most often eliminated by biotransformation and/or excretion into urine or bile. The liver is the major site for drug metabolism, but specific drugs may undergo biotransformation in other tissues.
- [Note: Some agents are initially administered as inactive compounds.]

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Kinetics of Metabolism

- First-Order Kinetics: The metabolic transformation of drugs is catalyzed by enzymes, and most of the reactions obey Michaelis-Menten kinetics.
  - V = rate of drug metabolism = $V_{max}[C]/K_m$
- In most clinical situations, the concentration of the drug, [C], is much less than Michaelis constant, K_m and the Michaelis-Menten equation reduces to:
  - V = rate of drug metabolism = $V_{max}[C]/K_m$
- That is, the rate of drug metabolism is directly proportional to the concentration of free drug, and first-order kinetics are observed.

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- Zero-Order Kinetics
  - V = rate of drug metabolism = $V_{max}[C]/[C] = V_{max}$
- The enzyme is saturated by a high free-drug concentration, and the rate of metabolism remains constant over time. This is called zero-order kinetics (or sometimes referred to clinically as nonlinear kinetics). A constant amount of drug is metabolized per unit of time.

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Reactions of Drug Metabolism

- The kidney cannot efficiently eliminate lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal tubules. Therefore, lipid-soluble agents must first be metabolized in the liver using two general sets of reactions, called Phase I and Phase II.

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- Phase I: Reactions function to convert lipophilic molecules into more polar molecules by introducing or unmasking a polar functional group.
- Phase I reactions utilizing the P450 system: The phase I reactions most frequently involved in drug metabolism are catalyzed by the cytochrome P450 system (also called microsomal mixed function oxidase).
- Drug + O_2 + NADPH + H+ ⇨ $Drug_{modified}$+H_2O+NADP
- The oxidation proceeds by the drug binding to the oxidized form of cytochrome P450, and then oxygen is introduced through a reductive step coupled to NADPH: cytochrome P450 oxicderoeductase.

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- Inducers: The cytochrome P450-dependent enzymes are an important target for pharmacokinetic drug interactions. One such interaction is the induction of selected CYP isozymes. Certain drugs, most notably phenobarbital, rifampin, and carbamazepine, are capable of increasing the synthesis of one or more CYP isozymes. The increased biotransformation rates can lead to significant decreases in plasma concentrations of drugs as measured by AUC, with concurrent loss of pharmacologic effect.

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- Inhibitors: Inhibition of CYP isozyme activity is an important source of drug interactions that leads to serious adverse events. The most common form of inhibition is through competition for the same isozyme.

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Phase II

- This phase consists of conjugation reactions.
- Glucuronidation is the most common and the most important conjugation reaction.

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Drug Elimination

- Removal of a drug from the body may occur via a number of routes, the most important being through the kidney into the urine. Other routes include the bile, intestine, lung, or milk in nursing mothers.

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Renal Elimination of a Drug

- Glomerular Filtration: Drugs enter the kidney through renal arteries, which divide to form a glomerular capillary plexus. Free drug (not bound to albumin) flows through the capillary slits into Bowman's space as part of the glomerular filtrate.
- Proximal Tubular Secretion: Drug that was not transferred into the glomerular filtrate leaves the glomeruli through efferent arterioles, which divide to form a capillary plexus surrounding the nephric lumen in the proximal tubule.
- Distal Tubular Reabsorption: As a drug toward the distal convoluted tubule, its concentration increases and exceeds that of the perivascular space.

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- Role of Drug Metabolism: Most drugs are lipid soluble and diffuse out of the kidney's tubular lumen when the drug concentration in the filtrate becomes greater than that in the perivascular space.
- To minimize this reabsorption, drugs are modified by the body to be more polar using two types of reactions:
  - Phase I reactions that involve either the addition of hydroxyl groups or the removal of blocking groups from hydroxyl, carboxyl, or amino groups.
  - Phase II reactions that use conjugation with sulfate, glycine, or glucuronic acid to increase drug polarity. The conjugates are ionized, and the charged molecules cannot back-diffuse out of the kidney lumen.

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Quantitative Aspects of Renal Drug Elimination

- Plasma clearance is expressed as the volume of plasma from which all drug appears to be removed in a given time – for example, as ml/min. clearance equals the amount of renal plasma flow multiplied by the extraction ration, and because these are normally invariant over time, clearance is constant.

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Excretion Rate

- Excretion Rate = (clearance)(plasma concentration)
- The elimination of ad rug usually follows first-order kinetics, and the concentration of drug in plasma drops exponentially with time. This can be used to determine the half-life of the drug (the time during which the concentration of the drug decreases from C to ½ C).
- $T_{½}$ = IN 0.55/K_e = 0.693 V_d/CL
- Where K_e = the first-order rate constant for drug elimination from the total body and CL = clearance.

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Kinetics of IV Infusion

- With continuous IV infusion, the rate of drug entry into the body is constant. In the majority of cases, the elimination of a drug is first-order; that is, a constant fraction of the agent is cleared per unit of time.

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- Steady-state drug levels in blood: Following the intiation of an intravenous infusion, the plasma concentration of drug rises until the rate of drug eliminated from the body precisely balances the input rate.

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- Influence of the rate of drug infusion on the steady-state: A steady-state plasma concentration of a drug occurs when the rate of drug elimination is equal to the rate of administration.
- Time required to reach the steady-state drug concentration: The concentration of drug rises from zero at the start of the infusion to its ultimate steady-state level C_{ss}. The fractional rate of approach to a steady-state is achieved by a first-order process.

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Exponential Approach to Steady-state

- The rate constant for attainment of steady-state is the rate constant for total body elimination of the drug, K_e. Thus, 50% of the final steady-state concentration of drug observed after the time elapsed since the infusion, t, is equal to $t_{½}$, where $t_{½}$ (or half-life) is the time required for the drug concentration to change by 50%. One can assume that a drug will reach steady-state in about four half-lives.

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Drug-Receptor Interactions and Pharmacodynamics

- Overview
  - Most drugs exert their effects, both beneficial and harmful, by interacting with receptors – that is, specialized target macromolecules – present on the cell surface or intracellularly. Receptors bind drugs and mediate their pharmacologic actions.

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- The formation of the drug-receptor complex leads to a biologic response, and the magnitude of the response is proportional to the number of drug-receptor complexes.
- Drug + Receptor ⇌ Drug-receptor complex → Biological effect

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Chemistry of Receptors and Ligands

- Interaction of receptors with ligands involves the formation of chemical bonds, most commonly electrostatic and hydrogen bonds, as well as weak interactions involving van der Waals forces. These bonds are important in determining the selectivity of receptors, because the strength of these noncovalent bonds is related inversely to the distance between the interacting atoms.

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Major Receptor Families

- Pharmacology defines a receptor as any biologic molecule to which a drug binds and produces a measurable response. Thus, enzymes and structural proteins can be considered to be pharmacologic receptors. The richest sources of therapeutically exploitable pharmacologic receptors are proteins that are responsible for transducing extracellular signals into intracellular responses. These receptors may be divided into four families:
  - Ligand-gated ion channels
  - G protein-coupled receptors
  - Enzyme-linked receptors
  - Intracellular receptors

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- Ligand-gated ion channels (ex: cholinergic nictonic receptors) = Changes in membrane potential or ionic concentration within cell = intracellular effect
- G Protein-coupled receptors (ex: B and A adrenoreceptors) = protein phosphorylation = intracellular effect
- Enzyme-linked receptors (ex: insulin receptors) = protein and receptor phosphorylation = intracellular effect
- Intracellular receptors (ex: steroid receptors) = protein phosphorylation and altered gene expression = intracellular effect

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Ligand-gated Ion Channels

- The first receptor family comprises ligand-gated ion channels that are responsible for regulation of the flow of ions across cell membranes.

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G protein-coupled receptors

- Comprised of a single peptide that has seven membrane-spanning regions, these receptors are linked to a G protein having three subunits, and A subunit that binds guanosine triphosphate (GTP) and a BY subunit.
- Second messengers: A common pathway turned on by G_s is the activation of adenylyl cyclase by A-GTP subunits, which results in the production of cyclic-adenosine monophosphate (cAMP), a second messenger that regulates protein phosphorylation. G proteins also activate phospholipase C, which is responsible for the generation of two other second messengers.

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Enzyme-linked Receptors

- A third major family of receptors consists of those that have a cytosolic enzyme activity as an integral component of their structure or function.

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Intracellular Receptors

- The fourth family of receptors differs considerably from the other three in that the receptor is entirely intracellular and, therefore, the ligand must diffuse into the cell to interact with the receptor.

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Dose-Response Relationships

- An agonist is defined as an agent that can bind to a receptor and elicit a response. The magnitude of the drug effect depends on its concentration at the receptor site, which in turn is determined by the dose of drug administered and by factors characteristics of the drug, such as rate of absorption, distribution, and metabolism.

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Potency

- A measure of the amount of drug necessary to produce an effect of a given magnitude.

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Efficacy

- The second drug property that can be determined from graded dose-response plots is the efficacy of the drug. Efficacy is dependent on the number of drug-receptor complexes formed, and the efficiency of coupling of receptor activation to cellular responses.

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Antagonists

- Antagonists are drugs that decrease the actions of another drug or endogenous ligand. Antagonism may occur in several ways.

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Partial Agonists

- Partial agonists have efficacies (intrinsic activities) greater than zero but less than that of a full agonist.

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Quantal Dose-Response Relationships

- Another important dose-response relationship is that of the influence of the magnitude of the dose on the proportion of a population that reasons. These responses are known as quantal responses, because, for any individual, the effect either occurs or it does not.

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Therapeutic Index

- The therapeutic index of a drug is the ratio of the dose that produces to the dose that produces a clinically desired or effective response in a population of individuals.
- Thus is a measure of a drug's safety, because a large value indicates that there is a wide margin between doses that are effective and doses that are toxic.

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Determination of Therapeutic Index

- The therapeutic index is determined by measuring the frequency of desired response and toxic response at various doses of the drug.

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Adverse Drug Reactions

- Absorption
- Distribution
- Metabolism
- Excretion
- In pharmacology any unexpected or dangerous reaction to a drug. An unwanted effect caused by the administration of a drug. The onset of the adverse reaction may be sudden or develop over time.

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Adverse Drug Reaction – Friend or Foe?

- Medrol dose-pack causing a steroid induced psychotic event – including mania and hypomania.
- You as a pharmacist are an expert in pharmacology.
- Backgrounds in chemistry – inorganic, organic, biochemistry, and organic medicinal chemistry.
- You are a unique professional.
- You are qualified to testify as an expert witness.

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- 1. Cortico-steroid induced psychotic event.
- 2. Chantix and Wellbutrin – resulting in a suicidal thought process.
- 3. Retrograde extrapolation of blood alcohol – vehicular homicide.
  - Advertise yourself and services to local lawyers – personal relationship and professional relationship.
  - Judge and prosecuting district attorney may not understand life science, clinical terms, and analogies.
  - Keep nomenclature in laymen's terms.
  - Stay ready to clarify and entertain questions!

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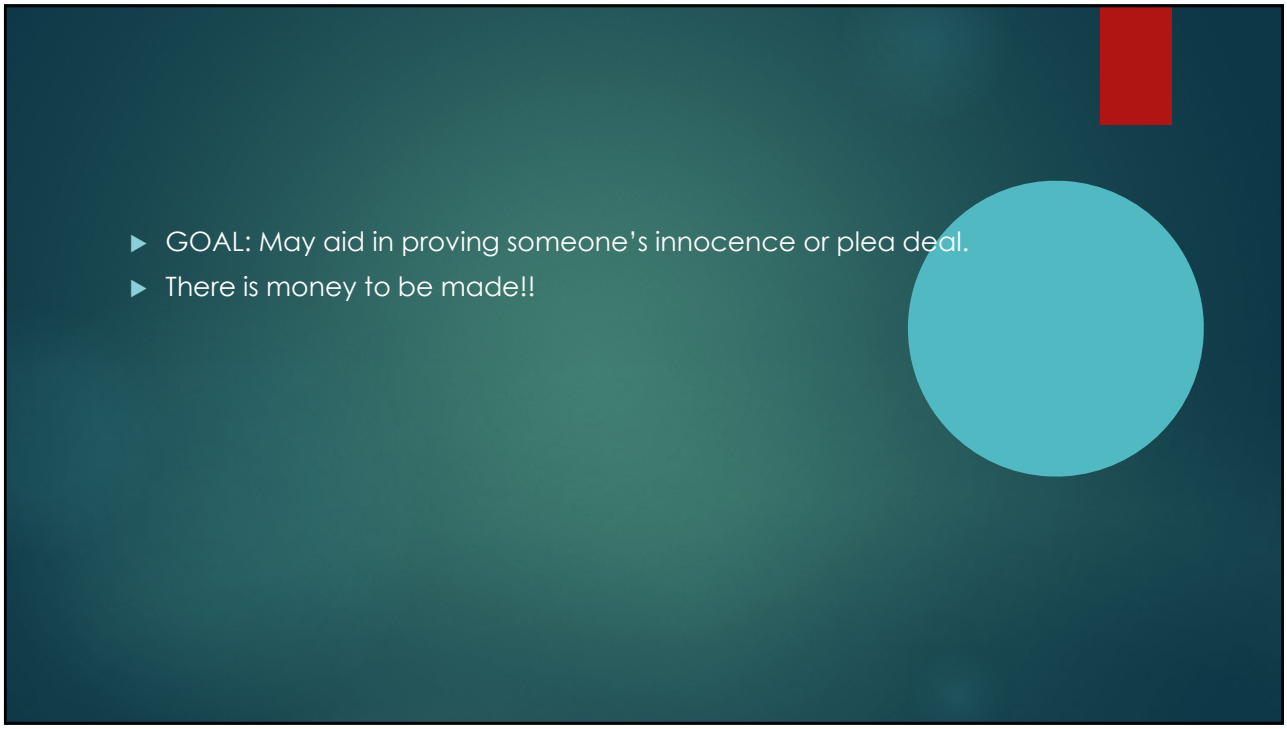
GOAL: May aid in proving someone's innocence or plea deal.
There is money to be made!!

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