PHARMACOLOGY

بسم الله الرحمن الرحيم

MID (Last Lecture) – Lecture 8

Pharmacodynamics (Pt.2)

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

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APPROVED
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Lecture 8

Pharmacodynamics of Drugs: Toxicity and Interactions

Understanding the Mechanisms of Action and Adverse Effects

For simplicity, pharmacology is the science that tells what will happen to the drug in the body (ingestion, effect and elimination).

Dynamics: effect of the Drug on the body.

Kinetics: effect of the body on the drug.

Introduction to Pharmacodynamics

Definition: Study of how drugs affect the body, focusing on mechanisms and biological responses.

Key Elements:

- Drug-receptor interaction
- Dose-response relationship
- Therapeutic window

Drugs are toxins that are taken in certain doses and frequency in order to induce its effects.

Further Introduction to Pharmacology

- When developing a drug, we typically focus on a well-characterized (well-studied) receptor in a specific organ and design the drug to fit it through a key-and-lock interaction. Additionally, we aim for the interaction to be reversible, allowing the drug to deactivate when no longer needed.

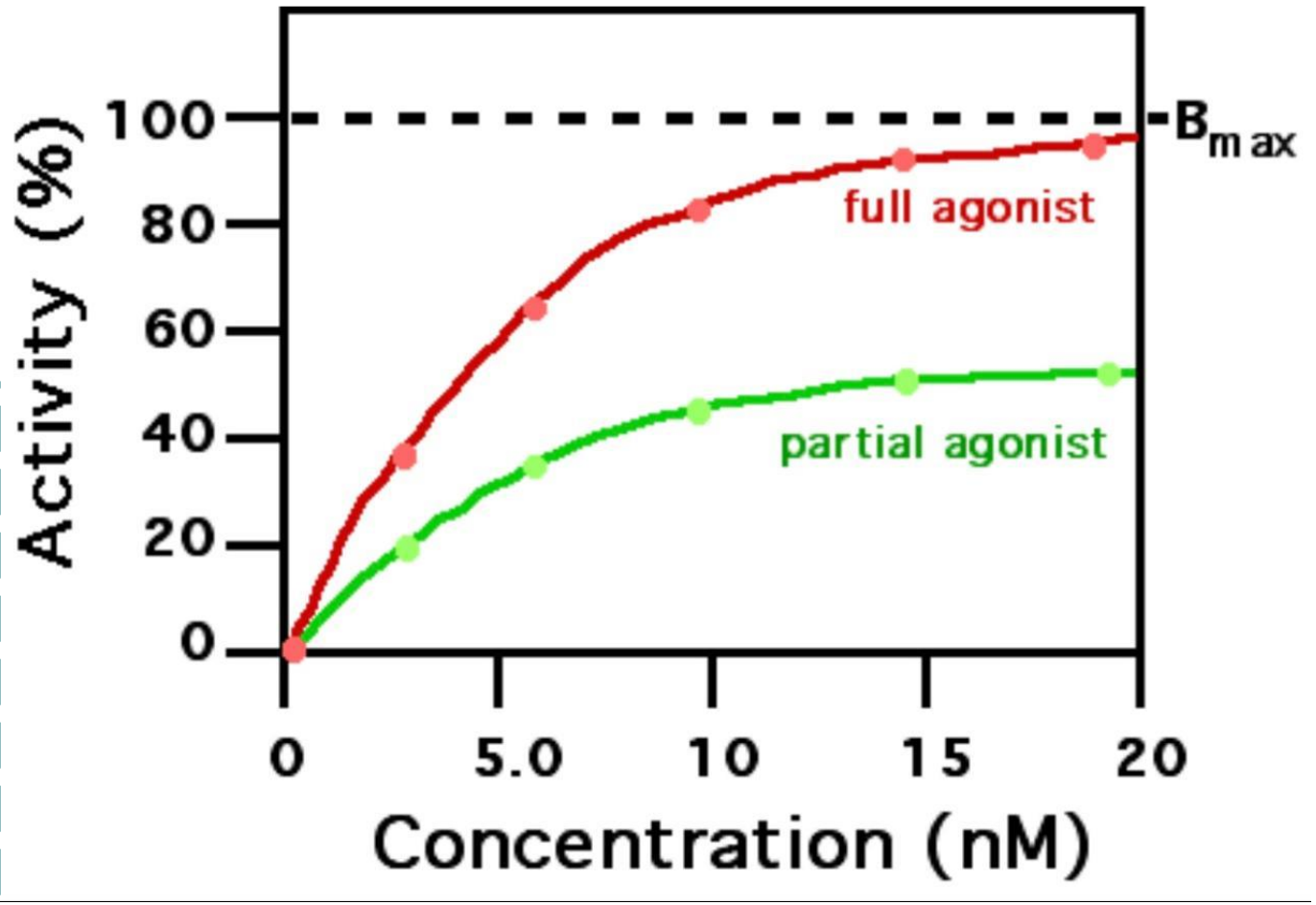
- When a drug-receptor interaction is irreversible, it often involves a covalent bond, with functional groups such as sulfhydryl (-SH) bond. This type of interaction is commonly associated with warfare agents, toxins, and certain poisonous mushrooms.
- For example: Sarine gas (it inhibits acetylcholinesterase)

- The dose-response relationship describes how administering a drug at a specific dose produces a corresponding effect. Increasing the dose typically enhances the effect, but this occurs only within a range bounded by the effective (therapeutic) dose and the toxic dose.

Mechanisms of Drug Action

- Types of drug effects:
- Agonists Ex: adrenaline-like drugs.
- Antagonists Anything that blocks a receptor: Ex: Atropine.
- Partial agonists

The ideal drug design targets a specific receptor for precise action.
For example, during relaxation and eating, the body enters the "rest and relax" or "rest and digest" state, activating the parasympathetic system and promoting the release of acetylcholine (ACh) from the intestines.
Note: ACh is closely associated with bodily secretions, including saliva, GI secretions, and mucus in the lungs.



Agonists

- **Definition**: Agonists are drugs or molecules that bind to a receptor and activate it, producing a biological response. They mimic the action of endogenous ligands (naturally occurring substances in the body, such as hormones or neurotransmitters).
- **Example**:
  - Morphine acts as an agonist at opioid receptors to provide pain relief.
- **Mechanism**: Full agonists produce the maximum possible response at a receptor.

A dive into adrenaline-like agonists:

- During the “fight or flight” response, your body diverts energy away from digestion, leading to reduced gastrointestinal activity. Key effects include mydriasis (pupil dilation), reduced secretions, xerostomia (dry mouth), bronchodilation (enhanced airflow), and increased heart contractility, especially in skeletal and cardiac muscles.
- Adrenaline, which binds primarily to Beta-2 receptors, plays a crucial role in this state by inducing bronchodilation and suppressing bodily secretions. In patients with COPD, Beta-2 agonists—drugs that mimic adrenaline—are used to induce bronchodilation because Beta-2 receptors are abundant in the airways.
- Inhalers are localized treatments that deliver Beta-2 agonists to relax airway smooth muscles, causing bronchodilation, and may also include anticholinergics like atropine to reduce secretions. The heart predominantly has Beta-1 receptors, but it also contains Beta-2 receptors. While Beta-2 receptors in the heart can theoretically be stimulated by inhalers, the doses used are minimal, and significant side effects like palpitations or increased heart rate are rare.
- To manage an acute asthma attack, an inhaler is the first-line treatment for immediate relief. In contrast, oral medications are used for long-term control, aiming to reduce the frequency of attacks—for example, decreasing their occurrence from twice a week to once a week.

Antagonists

- **Definition**: Antagonists are drugs or molecules that bind to a receptor but do not activate it. Instead, they block the receptor, preventing other substances (like agonists) from binding and eliciting a response.
- **Example**:
  - Naloxone is an antagonist at opioid receptors and is used to reverse opioid overdose.
- **Mechanism**: Antagonists can be classified into:
  1. **Competitive antagonists**: Compete with agonists for the same binding site on the receptor.
  2. **Non-competitive antagonists**: Bind to a different site on the receptor, preventing activation regardless of agonist concentration.

A dive into atropine, an antagonist:

- Atropine, derived from the Atropa belladonna plant, is an antagonist that specifically blocks muscarinic acetylcholine receptors.
- Atropine is widely used in medical practice to inhibit secretions and reduce smooth muscle activity. Some examples include:
    1. Dental procedures: Atropine is administered to reduce saliva production during dental procedures.
    2. Abdominal surgeries: It is used to decrease gastrointestinal (GI) motility, such as in colonoscopy or endoscopy.
    3. Chronic obstructive pulmonary disease (COPD): Atropine helps reduce excessive mucus secretion in the airways.
    4. Ophthalmology: Eye drops containing atropine are used to induce mydriasis (pupil dilation) for eye examinations.

Beta-1 Blockers, Antagonists:

- An example of an antagonist is a Beta-1 blocker. During a “fight or flight” reaction, the sympathetic nervous system triggers the release of adrenaline into the bloodstream, while acetylcholine (ACh) is degraded or reabsorbed. Adrenaline binds to Beta-1 receptors in the heart, increasing its contractility and heart rate to prepare the body for action.
- Beta-1 blockers are cardio-selective drugs that target Beta-1 receptors, which are predominant in the heart. By decreasing the heart’s contractility and heart rate, these blockers are used to treat high blood pressure (hypertension). For patients with atherosclerosis, where the blood vessels have a narrowed diameter and cannot tolerate high pressure, Beta-1 blockers reduce the force and rate of the heart’s contractions. This decreases blood pressure and reduces strain on the vessels.
- Beta-1 blockers (commonly ending in -lol, e.g., atenolol or metoprolol) are taken orally and are carefully dosed to block only a portion of the Beta-1 receptors. This ensures the heart continues to contract, but at a reduced rate and force, maintaining necessary cardiac output without stopping the heart entirely.
- Although Beta-1 receptors are primarily found in the heart, they are also present in the lungs, but in much smaller numbers. This means Beta-1 blockers have minimal effects on the lungs, making them suitable for most patients, including those without significant respiratory issues.

Partial Agonists

- **Definition**: Partial agonists are drugs or molecules that bind to a receptor and activate it but produce a weaker (sub-maximal) response compared to a full agonist, even at full receptor occupancy.
- **Example**:
  - Buprenorphine is a partial agonist at opioid receptors, providing pain relief with a lower risk of respiratory depression compared to full agonists.
- **Mechanism**: Partial agonists can act as:
  - Agonists in the absence of a full agonist.
  - Antagonists in the presence of a full agonist, by competing for the receptor and reducing the maximal response.

Partial Agonists

- Partial agonists can also exhibit mixed effects, acting as agonists in some contexts and antagonists in others. For example, a drug that is 50% agonist and 50% antagonist may activate a receptor partially but block a full agonist from producing its maximum effect. Similarly, a drug that is 70% agonist and 30% antagonist would provide stronger activation than the first example but still not act as a complete agonist. These drugs are therefore not purely agonists or antagonists but exhibit properties of both.

Toxicity of Drugs

Undesirable effects of drugs

Definition: Adverse effects resulting from excessive drug levels or sensitivity.

Types:

- Acute toxicity
- Chronic toxicity
- Organ-specific toxicity (e.g., Hepatotoxicity, Nephrotoxicity, Cardiotoxicity, Ototoxicity)

One of the causes of Cardiotoxicity is chemotherapy that ends with mycin. Ototoxicity is toxicity that affects the ears.

Examples: Overdose of paracetamol (acetaminophen) leading to liver damage (hepatotoxicity).

The safest drug is Panadol it can be taken during pregnancy, breast-feeding or even when the patient has stomach ulcers. However, an overdose of (8g) causes toxicity.

- Acute toxicity.
- Sometimes anaphylactic shock could occur, which is an over reactive allergic response
- Example: People with food allergies may experience anaphylactic shock, characterized by increased histamine levels in the blood, leading to bronchoconstriction, cardiovascular issues, and severe symptoms. When this happens, they are treated with an adrenaline shot (epinephrine), which counteracts the symptoms by relaxing airway muscles and stabilizing blood pressure.
- Chronic toxicity
- Occurs in long-term treatments, particularly with medications used for chronic diseases.
- Example: Anti-cholesterol and lipid-lowering drugs (statins) may cause liver or kidney damage, muscle pain (myopathy), fatigue, and weakness as side effects over time.

Drug Interactions

Dairy products can interfere with the absorption of certain antibiotics, particularly fluoroquinolones like ciprofloxacin and other drugs ending in "-floxacin."

Definition: When the effects of one drug alter another.

Types:

• Pharmacodynamic interactions (synergism, antagonism)

• Pharmacokinetic interactions (absorption, metabolism, elimination)

Examples: Warfarin and aspirin leading to increased bleeding risk.

- Alcohol is one of the biggest triggers of drug-drug interactions, eliminating the effect of antidepressants and oral contraceptives. Alcohol may increase the copies of cytochrome P450 enzymes, making the dose ineffective, or decrease the copies, making the dose toxic.
- Caffeine increases the effect of Panadol as it enhances the absorption of paracetamol. Another example is carbidopa and levodopa; carbidopa increases the effect of levodopa.

Clinical Examples of Drug Interactions

- Case studies: Grapefruit juice inhibiting drug metabolism, it prolongs its action (it stays longer in the body).
- Combining CNS depressants (e.g., alcohol + benzodiazepines) causing respiratory depression.

Like Xanax

Factors Influencing Toxicity and Interactions

- **Patient-specific factors**:
  - Age, genetics, comorbidities
- **Drug-specific factors**:
  - Narrow therapeutic index Like warfarin
  - Polypharmacy

Administration of too many drugs (**polypharmacy**) requires careful scheduling to prevent antagonistic interactions, ensure optimal effects, and avoid overdose. For example, drugs for cholesterol should be taken at night, as cholesterol metabolism and synthesis primarily occur during the night. On the other hand, aspirin and antihypertensive medications are often recommended in the morning, as the risk of strokes and heart attacks is higher during this time.

Preventing Toxicity and Managing Interactions

- Monitor therapeutic drug levels.
- Avoid unnecessary polypharmacy.
- Use drug interaction databases and tools.
- Patient education on proper drug use.

The drug doses for chronic diseases like diabetes and hypertension must be checked every 5 years

Conclusion

- In summary:
  - Pharmacodynamics is the foundation for understanding drug action and toxicity.
  - Importance of awareness and management of drug interactions.
- Future directions in personalized medicine.

By genetic analysis and studying the the genome and the cytochrome P450 of an individual.

Pharmacodynamics

Drug toxicity

1. Hepatotoxicity (Liver Toxicity)

- **Drugs**: Paracetamol (Acetaminophen)
  - **Mechanism**: Overdose leads to the depletion of glutathione and accumulation of toxic metabolites leading to liver cirrhosis which ends with, liver cell death.
  - **Clinical Example**: Acute liver failure in paracetamol overdose.

    Overdose of paracetamol is more than 8 grams a day.
- **Drugs**: Amiodarone
  - **Mechanism**: Direct mitochondrial damage and oxidative stress.
  - **Clinical Example**: Chronic liver disease with long-term use.

Cell respiration stops, leading to lactic acidosis in muscles and complete liver failure.

2. Nephrotoxicity (Kidney Toxicity)

- **Drugs**: Aminoglycosides (e.g., Gentamicin)
  - **Mechanism**: Accumulation in renal tubules causes oxidative damage and necrosis.
  - **Clinical Example**: Acute tubular necrosis. (irreversible damage)

    Aminoglycosides are antibiotics that typically have the suffix -mycin
- **Drugs**: Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
  - **Mechanism**: Inhibition of prostaglandin synthesis reduces renal perfusion.
  - **Clinical Example**: Acute kidney injury, especially in dehydrated patients.

    NSAIDs such as profen, ibuprofen.

3. Cardiotoxicity

- **Drugs**: Doxorubicin (Anthracycline class) used in chemotherapy.
  - **Mechanism**: Oxidative stress and damage to cardiac myocytes.
  - **Clinical Example**: Dilated cardiomyopathy.
- **Drugs**: QT-prolonging drugs (e.g., Amiodarone, Sotalol)
  - **Mechanism**: Disruption of cardiac ion channels, leading to arrhythmias.
  - **Clinical Example**: Torsades de Pointes (a type of polymorphic ventricular tachycardia)
  - These drugs are used to treat arrhythmias by increasing ECG QT interval.
  - Sotalol is a beta blocker.

- **4. Neurotoxicity**
- **Drugs**: Opioids (e.g., Morphine, Fentanyl)
  - **Mechanism**: Excessive CNS depression via activation of opioid receptors.
  - **Clinical Example**: Respiratory depression in overdose.
  - Opioids are used as pain relievers, overdosage of opioids (such as cocaine) leads to respiratoty depressioon and cardiac arrest.
- **Drugs**: Cisplatin an example of chemotherapy
  - **Mechanism**: Damages peripheral nerves by inducing oxidative stress and mitochondrial dysfunction.
  - **Clinical Example**: Peripheral neuropathy.

- **5. Hematotoxicity** **(blood formation by bone morrow is effected)**
- **Drugs**: Chloramphenicol
  - **Mechanism**: Suppression of bone marrow activity.
  - **Clinical Example**: Aplastic anemia.
- **Drugs**: Chemotherapeutic agents (e.g., Methotrexate)
  - **Mechanism**: Cytotoxic effects on rapidly dividing cells, including bone marrow.
  - **Clinical Example**: Pancytopenia.

- **6. Pulmonary Toxicity**
- **Drugs**: Amiodarone
  - **Mechanism**: Accumulation in lung tissue causes oxidative damage and fibrosis.

  Patients with COPD will face pulmonary fibrosis and emphysema.

  - **Clinical Example**: Pulmonary fibrosis.
- **Drugs**: Methotrexate
  - **Mechanism**: Inflammatory damage to alveoli.
  - **Clinical Example**: Hypersensitivity pneumonitis.

- **7. Gastrointestinal Toxicity**
- **Drugs**: NSAIDs (e.g., Ibuprofen, Aspirin)
  - **Mechanism**: Inhibition of prostaglandins disrupts mucosal protection.
  - **Clinical Example**: Peptic ulcers and gastrointestinal bleeding.

  That's why patients who take NSAIDs are advised to take them after meals.
- **Drugs**: Chemotherapy agents (e.g., 5-Fluorouracil)
  - **Mechanism**: Damage to rapidly dividing cells in the GI lining.(could also face diarreha)
  - **Clinical Example**: Severe mucositis.

- **8. Teratogenicity (affect the development of the fetus)**
- **Drugs**: Thalidomide
  - **Mechanism**: Disruption of embryonic development pathways.
  - **Clinical Example**: Limb malformations in newborns.
  - Thalidomide was used by pregnant women in the 1960s to treat morning sickness and other pregnancy-related symptoms. However, women who used the drug gave birth to babies with severe malformations (teratogenic effects), such as limb deformities (phocomelia). As a result, the drug was withdrawn from the market.
- **Drugs**: Isotretinoin
  - **Mechanism**: Interferes with cellular differentiation and proliferation.
  - **Clinical Example**: Severe birth defects (e.g., craniofacial abnormalities).

- **9. Ototoxicity**
- **Drugs**: Aminoglycosides (e.g., Gentamicin) antibiotics
  - **Mechanism**: Accumulation in cochlear hair cells leading to apoptosis.
  - **Clinical Example**: Hearing loss and tinnitus.
- **Drugs**: Cisplatin
  - **Mechanism**: Damage to auditory cells through oxidative stress.
  - **Clinical Example**: Sensorineural hearing loss.

Pharmacodynamics

Drug interactions

- **1. Additive Effects**
- **Definition**: When two drugs with similar actions combine to produce a greater effect **(1 + 1 = 2)**.
- **Example**: Both are blood thinners
  - **Drugs**: Aspirin + Warfarin ➔ Aspirin here refers to baby aspirin
  - **Mechanism**: Both inhibit clot formation (aspirin via platelet inhibition, warfarin via vitamin K antagonism).
  - **Clinical Outcome**: Increased risk of bleeding

Additive effect when both baby aspirin and warfarin are taken together.

Misconception:
Baby aspirin is not aspirin for babies. Instead, it indicates a small dose.
Baby aspirin → when aspirin is taken in small doses (80-100 mg) → it functions as an anticoagulant and blood thinner.
However, if aspirin is taken in larger doses (150-300 mg) → it functions as anti-inflammatory drug and pain killer.

- **2. Synergistic Effects**
- **Definition**: When two drugs enhance each other's effects **(1 + 1 > 2)**.
- **Example**: They have inhibitory effects on the CNS and cause respiratory depression
  - **Drugs**: Alcohol + Benzodiazepines (e.g., Diazepam)
  - **Mechanism**: Both act on GABA receptors in the CNS, enhancing sedative effects.
  - **Clinical Outcome**: Profound sedation and risk of respiratory depression.

- **3. Antagonistic Effects**
- **Definition**: When one drug reduces or inhibits the effect of another **(1 + 1 < 1)**.
- **Example**:
  - **Drugs**: Naloxone + Morphine
  - **Mechanism**: Naloxone is an opioid receptor antagonist and blocks morphine's analgesic and respiratory effects.
  - **Clinical Outcome**: Reversal of opioid overdose.

- Naloxone is used in rehabilitation of morphine addicts (Naloxone is an antidote for morphine).
- Addicts are given gradually increasing doses of naloxone while giving them gradually decreasing morphine doses.
- This combination causes the blockage of morphine opioid receptors causing a decline in morphine effects with time.

- **4. Potentiation**
- **Definition**: When one drug enhances the effect of another without having an effect itself.
- **Example**:
  - **Drugs**: Probenecid + Penicillin Or any penicillin-based antibiotic such as amoxicillin
  - **Mechanism**: Probenecid inhibits renal tubular excretion of penicillin, increasing its serum levels.
  - **Clinical Outcome**: Prolonged antibiotic effect.

Synergistic Effect VS Potentiation

- Synergist: one drug causes an increase in the effect of another drug while both drugs can individually cause a pharmacological effect (both drugs actually act).
- Potentiator: one drug aids in the increased effect of another drug while the potentiator itself cannot cause any direct effect (it only strengthens the other one).

- **5. Altered Drug Target Response**
- **Example**:
  - **Drugs**: Beta-Blockers (e.g., Metoprolol) + Beta-Agonists (e.g., Albuterol)
  - **Mechanism**: Beta-blockers antagonize the bronchodilatory effect of beta-agonists by blocking beta-2 receptors.
  - **Clinical Outcome**: Reduced efficacy of albuterol in treating asthma.

- **6. Toxicity Due to Interaction**
- **Example**: Digoxin is extracted from the digitalis plant
  - **Drugs**: Digoxin + Loop Diuretics (e.g., Furosemide) — Furosemide ⇔ Lasix (market name)
  - **Mechanism**: Diuretics cause hypokalemia, increasing digoxin binding to Na+/K+ ATPase, enhancing its effects.
  - **Clinical Outcome**: Increased risk of digoxin toxicity, including arrhythmias.

- Digoxin is used to treat congestive heart failure by increasing the heart contractility.
- Loop diuretics are used to treat hypertension by increasing fluid expel from the body which decreases the blood volume which in turn decreases the blood pressure.

- If a patient has both congestive heart failure (weak heart muscle) along with hypertension, other drugs must be used instead of loop diuretics to treat hypertension without causing the toxic effects of digoxin.

- **7. Enhanced CNS Depression**
- **Example**:
  - **Drugs**: Opioids (e.g., Morphine) + Antihistamines (e.g., Diphenhydramine)
  - **Mechanism**: Both depress the central nervous system.
  - **Clinical Outcome**: Increased drowsiness, impaired coordination, and respiratory depression.

- Natrium is Latin for Sodium → hypernatremia means high [Na^+]
- Kalium is Latin for Potassium → hyperkalemia means high [K^+]

- **8. Hyperkalemia Risk**
- **Example**: ACE: Angiotensin Converting Enzyme
  - **Drugs**: ACE Inhibitors (e.g., Enalapril) + Potassium-Sparing Diuretics (e.g., Spironolactone)
  - **Mechanism**: Both increase serum potassium levels.
  - **Clinical Outcome**: Severe hyperkalemia, leading to arrhythmias.

- Potassium-sparing diuretics are anti-hypertensive drugs that cause a decrease in blood pressure by the expel of fluids through urine without losing potassium from the body (and hence the name; they keep the potassium in the body but expel water by preventing the reabsorption of sodium and making water exit by osmosis due to high excretion of sodium).
- ACE inhibitors are also anti-hypertensive drugs that use a different mechanism.

- Overall, using both drugs together can cause hyperkalemia because of reduced water volume along with high potassium concentration.

- **9. Hypoglycemia Risk**
- **Example**:

Both are anti-diabetic

  - **Drugs**: Insulin + Sulfonylureas (e.g., Glipizide)
  - **Mechanism**: Both lower blood glucose through different mechanisms.
  - **Clinical Outcome**: Profound hypoglycemia, leading to confusion or seizures.

- **Summary of Clinical Implications:**
- **Importance of Awareness**: Drug interactions can enhance therapeutic effects or increase risks of adverse effects.
- **Strategies for Management**:
  - Avoid combining drugs with high interaction risks.
  - Adjust doses when interactions are unavoidable.
  - Monitor patients closely for signs of adverse effects.

- In adjusting the dose, we must account for the liver and kidney functions by doing appropriate tests before committing the patient to a treatment.

- As a physician, you must make sure that you take into consideration RISK vs BENEFIT.

  - If a drug treats a mild issue and can cause serious more dangerous and life-threatening problems elsewhere it must not be prescribed.
  - On the contrary, if a drug causes mild side effects while treating a major illness it is most probably worth it.

Thank you

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

رسالة من الفريق العلمي:

هذا في علاج الأبدان..

فماذا عن شفاء الأرواح والأبدان؟!

﴿ وَنُنَزِّلُ مِنَ ٱلْقُرْءَانِ مَا هُوَ شِفَآءٌ وَرَحْمَةٌ لِّلْمُؤْمِنِينَ ۙ وَلَا يَزِيدُ ٱلظَّٰلِمِينَ إِلَّا خَسَارًا ﴿٨٢﴾ ﴾

اللهم اجعل القرآن العظيم ربيع قلوبنا ونور صدورنا وذهاب همومنا وجلاء أحزاننا