PHARMACOLOGY

بسم الله الرحمن الرحيم

MID – Lecture 2

Pharmacodynamics

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

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Pharmacodynamics: How Drugs Affect the Body

Mechanisms of Drug Action

A few notes before you study our modified slides:

- The annotations written in dark blue are a combination of notes the Professor mentioned from several lectures. Therefore, you may find some notes that have not been mentioned in your section's lecture. However, our main resource was the recorded lecture on JU Medicine.
- In one of the section's lectures, a brief introduction was given on the remaining part of pharmacokinetics. Per the Professor's instructions, this portion will not be discussed here; we will explore it in further detail next week.

Samar Hunaiti

Introduction to Pharmacodynamics

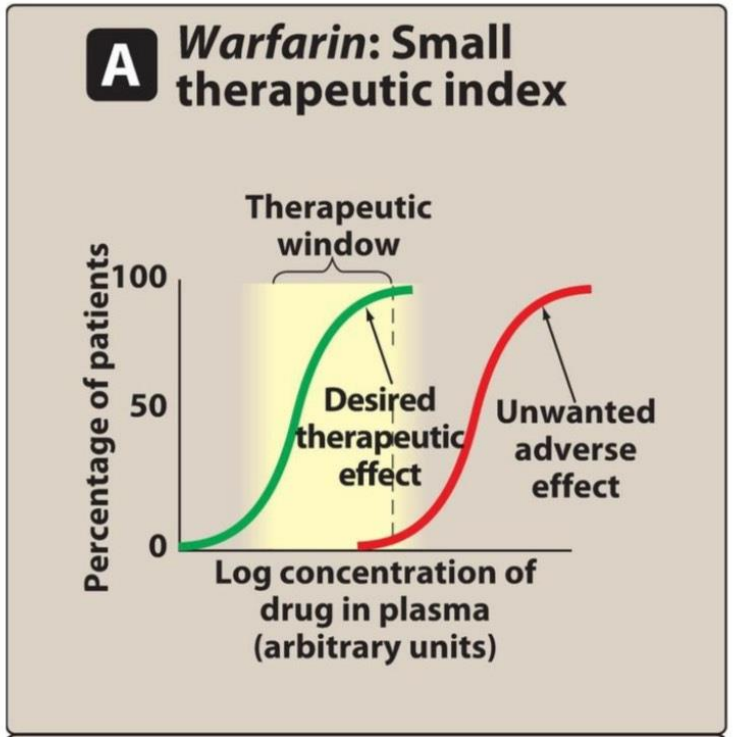
Recall that there are two main branches to pharmacology: pharmacokinetics (effect of body on drugs) and pharmacodynamics (effect of drug on body)

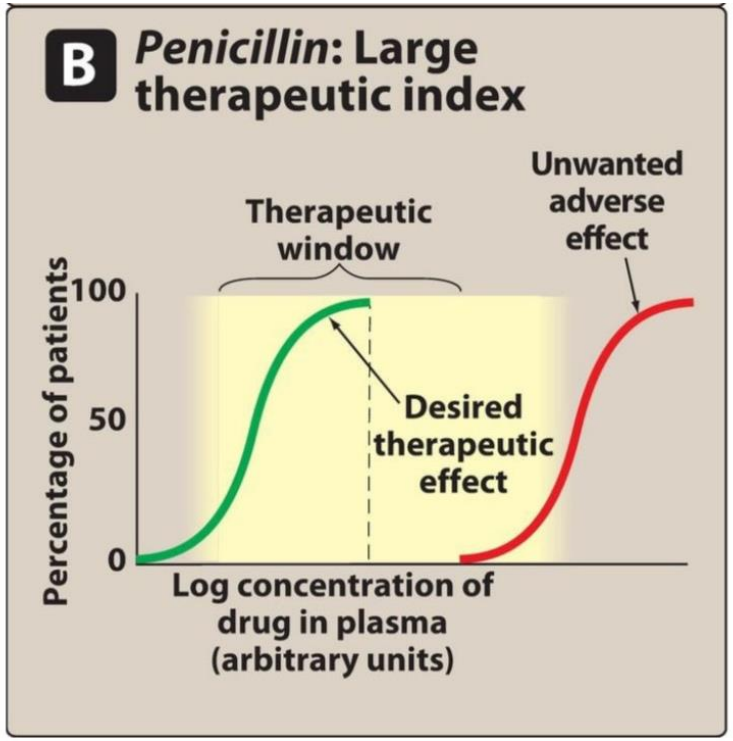
- Definition: Pharmacodynamics is the study of how drugs exert their effects on the body, including:
  - mechanisms of action
  - drug-receptor interactions. Drug-receptor interactions are very specific, just like the lock-and-key mechanism we discussed in biochemistry lectures. This allows the drug to act on very specific locations in the body
- Importance: Understanding pharmacodynamics helps predict the effects of a drug
  - at different doses. (see next slide)
  - in different patients. For example, children and adults require different doses.

Importance of controlling dosage (added slide)

- Drugs are toxins, so they must be administered at calculated doses.
- There is a concept known as the therapeutic window/index, in which every drug has a dose margin which cannot be exceeded:
  - Below this margin, the dose is considered ineffective and of no benefit to the patient.
  - Once this margin is exceeded, the dose becomes toxic/lethal.
  - Therefore, when assigning doses, we must make sure we stay within this therapeutic window (**see slide 13 for more clarification**)
- When we create a drug, we aim to keep its therapeutic window as wide as possible. This minimizes the chances of lethality if the dose is miscalculated, or if the patient forgot that they had already taken their medication and accidentally took more than the required dose.

The therapeutic index, illustrated[1] (added slide)





Warfarin is a drug given to patients with congestive heart failure to increase the contractility of the heart. Another drug that does this is Digoxin. It has a relatively small therapeutic window.

Penicillin is an antibiotic. It has a relatively large therapeutic window.

The concept of potency (added slide)

- Potency is a measure of the strength/concentration of a drug.
- A more potent drug only needs to be given at a low dose to achieve the required effect.
- For example, if drug A needs to be administered at a dose of 5 mg to achieve the same effect as would drug B at 50 mg, then drug A is more potent than drug B; we need to administer drug B at a dose x10 that of drug A!
- Drugs that have high potency tend to have narrower therapeutic windows, such as Warfarin and Digoxin. These drugs are not desirable because it becomes easier to reach the lethal dose, but we need them.
- This is why pateints who take very potent drugs should not take an extra dose if they forget whether or not they had already taken their medication for the day. Taking twice the required dose may be lethal.

Drug-Receptor Interactions (Part 1)

- Definition: Drugs interact with receptors on or within cells to exert their effects.
- Receptor: A protein that binds to a drug to initiate a biological response.

- We like drugs that bind to specific receptors on specific organs as they allow for direct, selective, and specific treatments.
- Such drugs have been used in breast cancer and prostate cancer therapies, in which the drug is complementary to receptors found exclusively on the breast/prostate.
- This means that, no matter how much the drug circulates in one's bloodstream, it will act on the breast/prostate only. This minimizes the side effects of the drug on other organs.
- However, most drugs we currently use are not selective nor specific, as the receptors to which they bind are found on many organs.
- For example, Revanin and Panadol circulate in the bloodstream and enter all organs, binding to wherever their receptor is found. This explains why these same drugs can treat a toothache or backache.

Drug-Receptor Interactions (Part 2)

- Affinity: The strength of the drug-receptor binding.
- We like drugs to have a high affinity to their receptor.
- To make this possible, scientists can use 3D and 4D techniques to visualize the structure of a receptor, create several drugs that are complementary to the receptor, and choose the candidate that binds the most strongly
- Even when the desired receptor is found on several organs, scientists can create drugs that bind with higher affinity to their receptor on a specific organ.

- Efficacy: The ability of a drug to produce a desired effect once bound to a receptor.
- Efficacy describes the effectivity of a drug.
- For example, the efficacy of pain-killers such as Revanin and Panadol is assessed through their ability to eliminate pain.
- Note that efficacy and potency are not synonymous; a more potent drug is not necessarily more efficacious.

Types of Receptors

*They will be discused later in more details

- Ion Channel Receptors: E.g., GABA, nicotinic receptors. This is based on attraction between positive and negative charged.
- G-protein Coupled Receptors (GPCRs): E.g., adrenergic receptors.
- Enzyme-linked Receptors: E.g., insulin receptors.
- Intracellular Receptors: E.g., steroid hormone receptors. Steroid hormones include estrogen, progesterone and testosterone. The drug must enter the cell in order to bind to the receptor.
- Example: How morphine (a GPCR (G-protein coupled receptor) agonist) binds to opioid receptors to relieve pain, for example in cancer patients. Opioid receptors are found exclusively in the brain. Therefore, morphine will only act on the brain once it crosses the blood-brain barrier, regardless of how much it circulates in the blood before that.

Agonists, Antagonists, and Partial Agonists – Part 1

- The purpose of pharmacology is to return pathology to physiology. This means that we use drugs to return abnormal conditions back into the norm (e.g. by returning high blood pressure to normal blood pressure).
- We have to be smart when designing drugs. For example, our blood vessels are naturally elastic. They expand as blood surges through them and recoil after the blood passes. In atherosclerosis, blood vessels become plastic (not elastic anymore) due to the buildup of cholesterol deposits inside them, forming a white layer and leaving less room for blood to flow. This happens with age as a result of a poor, uncontrolled diet rich in cholesterol.
- Although blood vessels can no longer stretch and recoil, and their diameter is reduced, the volume of blood that needs to move through them remains the same. As a result, resistance increases, blood pressure increases and arteries become prone to explosion.
- To prevent arteries from exploding, we need to lower the blood pressure. We already know that the stimulation of β1 receptors on the heart increases contractility, for example during a fight-or-flight response when adrenaline is released. Hence, we invented beta blockers, which block these beta receptors, therefore reducing the contractility of the heart and lowering blood pressure.

Physics 105 Recall:

$$V = \frac{\pi \, \Delta p \, r^4 \, t}{8 \, \eta \, L}$$

- **V:** *volume of the liquid*
- **r:** *radius of vessel*
- **t:** *time*
- **η:** *coefficient of viscosity*
- **Δp:** *change of pressure*
- **L:** *vessel lenght*

- ✓ Cholesterol deposits build up
- ✓ Diameter of vessels decreases
- ✓ Volume of blood remains constant
- ✓ The pressure increases

Agonists, Antagonists, and Partial Agonists – Part 2

- Agonist: A drug that binds to a receptor and activates it (e.g., adrenaline).
  - Agonists are similar to molecules in the body and produce the same effect.
  - Some drugs may be partial agonists, meaning they do not completely bind to receptors and produce a partial effect (only 80%, 50% or 25% of the effect produced by the similar molecule in the body, for example).
  - Examples of agonists include β2 stimulants in inhalers, which are used in the case of asthma because, like adrenaline, they bind to β2 receptors and cause bronchodilation.
  - In inhalers, the β2 stimulant molecules are nanoparticles that act on the respiratory system without entering the circulation. This is useful as we do not want them to block β2 receptors on the heart (recall that the heart has mostly β1 receptors, though some β2 receptors are present).
  - β2 stimulants bind 100% to beta-2 receptors. Other beta stimulants are partial agonists; they can bind to both beta-1 and beta-2 receptors, but only produce 80% of the effect.

Agonists, Antagonists, and Partial Agonists – Part 3

- Antagonist: A drug that binds to a receptor but does not activate it, blocking agonist action (e.g., beta-blockers).
  - Their effect is opposite to that of normal molecules in our bodies.
  - Examples include beta blockers (drugs that end with –lol). They are antihypertensive, cardioprotective drugs that do the opposite of what adrenaline does; adrenaline increases heart contractility while beta blockers reduce it by blocking the receptors to which adrenaline binds (β1 receptors).
  - Since beta-1 receptors are found mostly on the heart, designing drugs that only block β1 receptors means that we can ensure that they act on the heart.
- Partial Agonist: A drug that binds and partially activates a receptor (e.g., buprenorphine).

Dose-Response Relationship

- Definition: The relationship between the drug dose and the magnitude of the drug's effect.
- Threshold dose: The smallest dose that produces an effect. Also known as the effective dose. With time, the threshold dose of a drug may increase for some people. This happens if they take the drug in high doses for too long, causing them to develop tolerance.
- Maximum efficacy: The greatest effect a drug can produce, regardless of dose but before it hits the lethal dose.
- Potency: The amount of drug needed to produce a given effect.

Therapeutic Window and Index

- Therapeutic Window: The range of drug doses that produces a therapeutic response without causing significant adverse effects. Recall that it is the margin between the effective dose and the lethal dose. A drug such as paracetamol, which is effective at 500 mg yet lethal at 8 g is considered to have a wide therapeutic window, as the margin between the effective and lethal doses is large. Other drugs have a narrow therapeutic window. An example is a drug with an effective dose of 5 mg and a lethal dose of 15–20 mg. These drugs must be administered carefully, as any slight mistake by the doctor or patient may result in the patient accidentally taking a lethal dose.
- Therapeutic Index (TI): The ratio between the toxic dose and the therapeutic dose of a drug.
- Wide TI: Safe drug (e.g., penicillin).
- Narrow TI: Narrow safety margin (e.g., warfarin).

Pharmacodynamic Variability – Part 1

- Patient-Specific Factors: Age, genetics, disease state, and tolerance.
- Liver function and kidney function tests are necessary before prescribing any drug to ensure that the patient is capable of metabolism/detoxification (liver) and clearance/excretion (kidney), and dosage is determined accordingly. In people with liver failure/cirrhosis, the drug circulates in the body for longer and therefore leaves more side effects.
- Drug Interactions:
  - Synergistic effects (when drugs enhance each other).
    - Sometimes, drugs cannot achieve the desired effect on their own; they may need boosters (other drugs to enhance their function).
    - An example is salts being combined with antibiotics to boost their effect.
    - Another example is the combination of carbidopa and levodopa to manage the symptoms of Parkinson's disease. Levodopa works by being converted to dopamine in the brain. Carbidopa works by preventing levodopa from being broken down before it reaches the brain.[2] We say that carbidopa has a synergic effect.
  - Antagonistic effects (when drugs oppose each other).

Pharmacodynamic Variability – Part 2

- Drug Interactions:
  - Synergistic effects (when drugs enhance each other).
  - Antagonistic effects (when drugs oppose each other).
    - It is contraindicated to take certain drugs together, as drug-drug interactions may prevent them from working properly.
    - Alcohol is one of the biggest triggers of drug-drug interactions, eliminating the effect of antidepressants and oral contraceptives.
    - This is why patients must be asked what drugs they are already on as part of their medical history before being prescribed new drugs. Synergistic effects may be undesirable as well.
    - Sometimes, food-drug interactions may occur. Grapefruit and grapefruit juice cannot be taken with anticoagulants such as heparin as they inhibit their effect.
    - The same applies to macrolide antibiotics (antibiotics that end with -mycin, such as azithromycin and erythromycin),[3] which are cancelled out by dairy products.

Examples of Pharmacodynamic

- Concepts in Clinical Practice
- Example 1: Antihypertensives (beta-blockers) decrease blood pressure by blocking beta-1 adrenergic receptors found on the heart.
- Example 2: Anticoagulants (warfarin) inhibit vitamin K-dependent clotting factors. Deep vein thrombosis (DVT) occurs when a blood clot (thrombus) forms in one or more of the deep veins in the body, usually in the legs.[4] People who are sedentary for a long time (e.g. on a long flight or car ride) are prone to DVT regardless of age and are therefore advised to take baby aspirin or heparin as an anticoagulant, and to keep moving their legs as the contraction of calf muscle stimulates venous return (gets blood flowing from toe to head).
- Example 3: Insulin binds to receptors on muscle and fat cells to facilitate glucose uptake. In insulin resistance, cells are no longer sensitive to insulin and glucose uptake stops, so blood glucose levels remain very high. This is what happens during the pre-diabetic stage.

Conclusion

- Summary: Pharmacodynamics explains how drugs exert their effects through receptor binding, efficacy, and potency.
- Final Thought: Understanding pharmacodynamics helps optimize drug therapy for individualized patient care (e.g. targeting specific organs to minimize side effects, as previously described in the context of breast and prostate cancers).

Take home message

Pharmacodynamics: is how drugs affect the body via diverse mechanisms of drug action

Test yourself (added slide)

2.2 If 1 mg of lorazepam produces the same anxiolytic response as 10 mg of diazepam, which is correct?

A. Lorazepam is more potent than is diazepam.
B. Lorazepam is more efficacious than is diazepam.
C. Lorazepam is a full agonist, and diazepam is a partial agonist.
D. Lorazepam is a better drug to take for anxiety than is diazepam.

Correct answer = A. A drug that causes the same effect at a lower dose is more potent. B and C are incorrect because without information about the maximal effect of these drugs, no conclusions can be made about efficacy or intrinsic activity. D is incorrect because the maximal response obtained is often more important than the amount of drug needed to achieve it.

2.3 If 10 mg of oxycodone produces a greater analgesic response than does aspirin at any dose, which is correct?

A. Oxycodone is more efficacious than is aspirin.
B. Oxycodone is less potent than is aspirin.
C. Aspirin is a full agonist, and oxycodone is a partial agonist.
D. Oxycodone and aspirin act on the same drug target.

Correct answer = A. Drugs with greater response at maximally effective concentrations are more efficacious than drugs with a lower maximal response. Choice B is incorrect since no information is given about the half maximal concentrations of either drug. Choices C and D are incorrect since it is not known if both drugs bind to the same receptor population.

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			

Additional Resources:

رسالة من الفريق العلمي:

احذر أن تكون (أبا شبر):
فقد قيل: العلم ثلاثة أشبار، من دخلَ الشبر الأول؛ تكبر، ومن دخل في الشبر الثاني؛ تواضع، ومن دخل في الشبر الثالث؛علم أنه ما يعلم.
حلية طالب العلم، الفصل السابع

References Used:
(numbered in order as cited in the text)

1. Lippincott Illustrated Reviews Pharmacology 7th edition ,Page 112
   https://medlineplus.gov/druginfo/meds/a601068.html#:~:text=Levodopa%20is%20in%20a%20class,before%20it%20reaches%20the%20brain.
2. https://www.ncbi.nlm.nih.gov/books/NBK551495/#:~:text=Continuing%20Education%20Activity,sinusitis%2C%20pharyngitis%2C%20and%20tonsillitis.
3. https://www.mayoclinic.org/diseases-conditions/deep-vein-thrombosis/symptoms-causes/syc-20352557#

Extra References for the Reader to Use:

1. Lippincott Illustrated Reviews Pharmacology 7th edition , chapter 2