Pharmacotherapeutics

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Purpose:

The purpose of this course is to familiarize the nurse with the principles of pharmacology, including pharmacotherapeutics, pharmacokinetics, and pharmacodynamics.

Goals:

Upon completion of this course, the nurse should be able to:

- List at least 10 things that should be considered when assessing a patient.
- Describe the 7 steps to pharmacotherapeutics.
- Describe 7 types of drug therapy.
- Discuss 3 mechanisms by which drugs pass through membranes.
- Discuss absorption in 8 routes of administration.
- Discuss distribution, including the difference between protein-bound and free drug molecules.
- Explain how drug-drug reactions relate to protein-bound drug molecules.
- Explain 2 phases of metabolism.
- Discuss 5 factors that affect metabolism.
- Discuss how grapefruit effects drug metabolism.
- List 7 routes of drug excretion.
- Discuss at least 5 pharmacokinetic factors.
- Describe 3 mechanisms by which drug molecules bring about therapeutic response.
- Discuss the frequency distribution curve and the meaning of the ED50 point.
- Explain the meaning of the therapeutic index and the difference between ED50 and LD50.
- Discuss the therapeutic index and the margin of safety.

Introduction:

Throughout history people have used herbs for healing purposes. As early as 3500 BC, medical treatments were used in China as part of traditional Chinese medicines. The recipes for these medications were written down, and many are still in use today. Other cultures, such as the Egyptians, Indians, Greeks, and Romans had similar traditions. The active ingredients found in these traditional treatments are often the same ones used to formulate current drugs.

During the Dark Ages in Europe, the idea that sickness was punishment for sins may have slowed the development of medicines, but during the Renaissance, opium was introduced and then laudanum (a mixture of opium and herbal ingredients). These drugs were widely used for all types of ailments until the 19th century when the science of chemistry led to the development of many other drugs—a process that continues. The challenge now, with so many types of medications available, is to choose the right drug to meet the needs of the patient and to understand how drugs work.

Principles of pharmacology:

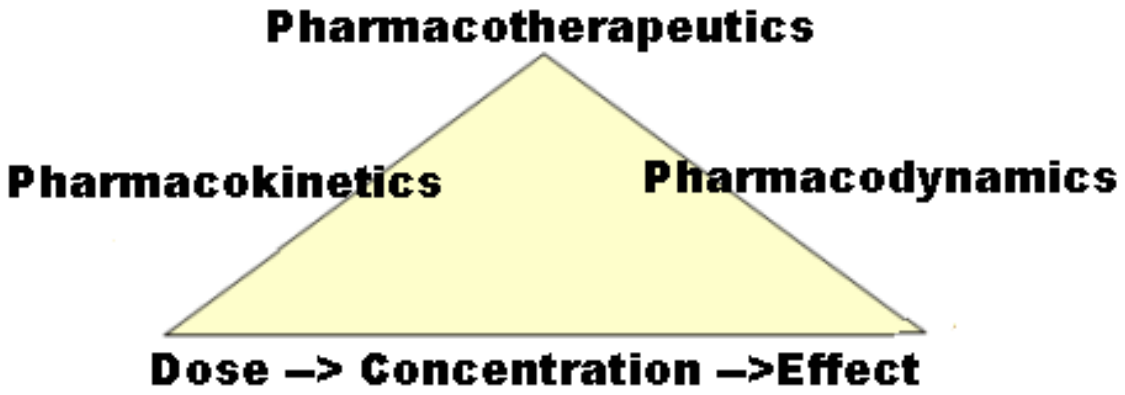
In the United States, drugs were not regulated until passage of the *Pure Food and Drug Act* in 1906. The purpose of this act was to prevent the manufacture, sale, and transportation of foods, drugs, medicine, and liquors that were adulterated, misbranded or poisonous.

While the original act was pretty weak, over time the bureau it established evolved into the Food and Drug Administration (FDA), which now has regulatory authority over drugs (animal and human), foods, preservatives, medical devices, biologics, and vaccines.

Because of the role of the FDA in drug safety, it is assumed that drugs on the market are safe, but the long-term effects of drugs cannot always be predicted. This led to the thalidomide crisis where the drug was used to relieve nausea associated with pregnancy but led to infants being born

without limbs. Thus, the healthcare provider must take precautions when prescribing medications, make informed decisions about drugs, and have a clear understanding of pharmacologic principles.

Pharmacotherapeutics:



Pharmacotherapeutics refers to the use of drugs to prevent, treat, and diagnose disease as well as to alter normal functions (such as preventing pregnancy). Pharmacotherapeutics correlates pharmacokinetics and pharmacodynamics with the microbiologic or biochemical aspects of disease.

As part of the process of administering drugs to patients, the healthcare provide must determine what the expected outcome will be. Thus, if an antibiotic is prescribed, a reduction in infection is the expected outcome. In order to determine the effectiveness of a drug, the outcome should be measurable in some way: through observation (decreased inflammation), patient reports (less pain), and/or assessment (decreased WBC count).

Even though two patients may have the same diagnosis, this does not necessarily mean that the same treatment or medication is indicated. When assessing a patient's need for medications and choosing the best medication for the patient, the healthcare provider must consider many issues:

- the condition for which the patient is to be treated.
- the patient's current drugs (including prescribed, over-the counter medications, and illicit drugs).
- possible drug interactions that may occur.
- contraindications.
- patient's mental status and ability to comply with directions.
- need for followup testing (such as periodic blood tests).
- costs of the drug and whether or not the patient has insurance to cover these costs.

- patient's social history (homeless status, presence or absence of support system, access to transportation or other services).
- pregnancy or breastfeeding status.
- the route of administration (oral, rectal, parenteral).
- absorption, distribution, metabolism, and excretion of drug.
- adverse effects of drugs.
- current medical conditions that may affect drug activity (such as kidney or liver disease).

Based on the assessment of the patient, the following **pharmacotherapeutic steps** are indicated:

1. Define the patient's problem for which treatment is indicated.
2. Outline the therapeutic objective.
3. Choose the appropriate treatment based on current practice and evidence-based research.
4. Verify the suitability of the chosen treatment.
5. Begin treatment.
6. Provide information to the patient and caregivers about the drug, instructions for use, and any precautions.
7. Carry out ongoing assessment and continue, modify, or stop treatment.

Pharmacotherapeutics encompasses many different **types of therapy,** some of which may overlap:

- **Acute therapy**: This type of therapy is indicated with acute, sudden and/or critical illnesses, such as pneumonia or cancer. Acute therapy usually needs to begin immediately if the patient is to improve or recover. Treatment is often more intense and may involve multiple drugs and ongoing assessment. Examples of acute therapy include epinephrine for anaphylaxis and chemotherapy for cancer.

- **Chronic/Long-term/Maintenance:** This type of therapy is intended for maintenance and to prevent a patient's condition from worsening or to control symptoms but not generally expected to bring about a cure. Patients with chronic disease, such as diabetes (insulin), bipolar disorder (lithium), and heart disease (diuretic, beta-blockers), may need to take medications for many years and often for the rest of their lives.

  Maintenance therapy may also be used to replace other drugs, such as long-term treatment with methadone to reduce heroin use. Long-term

therapy may also be indicated for non-illness-related reasons, such as oral contraceptives to prevent pregnancy and hormone therapy for transgender individuals.

- **Replacement therapy:** This type of therapy serves to replace something that is missing in the body and often critical, such as insulin. Some replacement therapy is needed throughout the patient's life, but others, such as hormone replacement therapy, may be used for a period of months or years to relieve symptoms. Replacement therapy may also be used to treat deficiencies of vitamins and minerals, such as vitamin D replacement therapy and iron for iron-deficiency anemia.

- **Palliative therapy:** This type of therapy is intended to provide comfort rather than cure. Palliative therapy is often used in the late stages of disease, such as cancer and heart disease. Palliative therapies include:
    - Analgesics (such as ibuprofen and opioids) to relieve pain and dyspnea.
      Anti-emetics (such as metoclopramide) to relieve nausea and vomiting.
    - Benzodiazepines (such as diazepam and lorazepam) to relieve anxiety.
    - Stool softeners (such as docusate sodium) to relieve constipation
      Antidepressants (such as amitriptyline and fluoxetine) to relieve depression.
    - Antidiarrheals (such as loperamide) to relieve diarrhea
    - Steroids (such as dexamethasone) to relieve anorexia and fatigue
    - Antimuscarinic agents (such as hyoscine butylbromide) to reduce respiratory secretions.

- **Supportive:** This type of therapy is intended to maintain body functions while the patient recovers from disease or injury. This may include the administration of packed red bloods for a patient with blood loss, electrolytes to provide the electrical energy needed for many body functions, and IV fluids for dehydration.

- **Prophylactic therapy:** This therapy is intended to prevent disease rather than treat or cure existing disease. Prophylaxis may include peri-surgical administration of antibiotics, rabies injection after exposure to a potentially rabid animal, routine vaccinations, and antiretroviral medications after exposure to HIV.

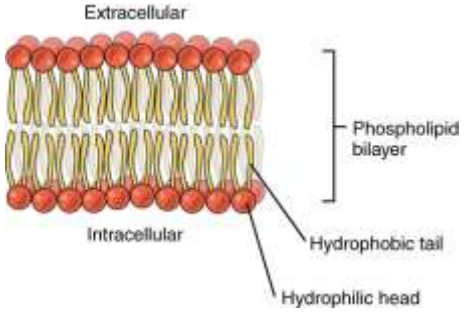
- **Empiric therapy:** This therapy is administered based on probabilities that a disease exists in the absence of confirming data. For example, if a patient has signs of a MRSA or *clostridium difficile* infection, immediate treatment may begin before the culture and sensitivities can confirm the diagnosis. Empiric therapy is often given based on symptoms when patients are in critical condition and a diagnosis has not yet been formulated.

Pharmacokinetics:

Once a drug has been chosen and administered, then the pharmacokinetics, what happens once the drug is in the patient's body, is of primary concern. Knowledge of pharmacokinetics of drugs is essential to maximize the benefits of drugs and minimize risks.

Pharmacokinetics depends on the movement of drugs across various membranes, which often have cells that are close together, requiring that drugs pass through the cells rather than between them. Membranes are comprised of double layers of phospholipids (fats containing phosphates).

Drugs can **pass through membranes** by the following mechanisms:



- Passing through channels or pores: Because the channels and pores are very small, generally only small ions, such as sodium and potassium, are able to pass through.

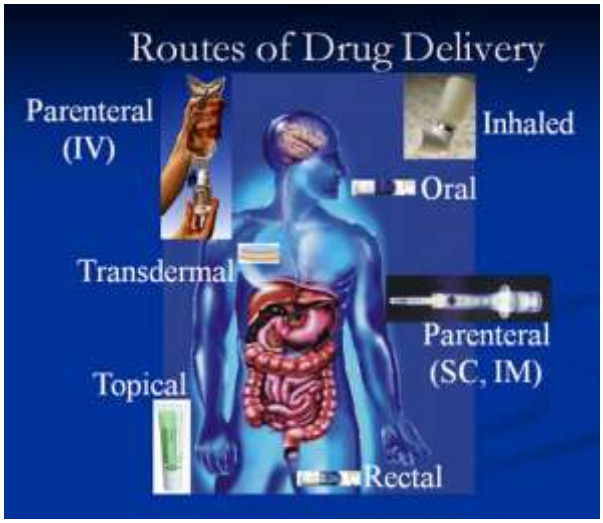
- Utilizing a transport system: One common transporter is P-glycoprotein, which transports many drugs out of cells. For example, it transports drugs out of kidney cells and into the urine. Transport systems are selective and will only transport some drugs, not all, based on the structure of the drug.

- Directly penetrating the membrane: This is the most common mechanism. In order to directly penetrate a membrane, the drug must be lipid soluble (lipophilic/hydrophobic) because the membrane is composed of phospholipids.

There are four steps to pharmacokinetics:

Step 1: Absorption
Absorption is the movement of a drug from its route of administration into the blood stream from where it is distributed to the tissues. The

bioavailability of a drug refers to how much of it is absorbed into the bloodstream. The bioavailability depends not only on the chemical structure of the drug but also the **route of administration**:



- Intravenous: Bioavailability is 100% because the drug is deposited directly into the bloodstream, so absorption takes place instantly. An advantage is that the blood level of the drug can be precisely calculated. The onset of action is generally rapid, so this route is especially valuable for emergency situations when time is a critical element.

  The drug, however, must be water soluble, so some drugs cannot be administered IV; but drugs that are weakly water soluble and require large volumes of fluid to dissolve, making them impractical for IM or SQ administration, can be administered by IV. A disadvantage of IV administration is that the effects are often irreversible. Risks associated with IV administration also include infection and embolism.

- Intramuscular, subcutaneous, and intradermal: Absorption is through the walls of capillaries into the bloodstream, but capillaries tend to have large spaces between cells so most drugs can pass easily through these spaces and don't have to penetrate membranes. There is little difference in the rates of absorption between IM and SQ although muscles tend to have a better blood supply, so IM may be slightly faster than SQ.

  The rate of absorption depends on how water soluble the drug is and on the blood supply—the better the blood supply, the faster the absorption. Drugs that are highly water soluble may absorb in 10 to 30 minutes while those that are weakly water soluble may take several hours.

  IM medications can also be formulated as *depot preparations,* which allows the drug to be slowly absorbed over long periods of time, such as days, weeks, or months. Examples of depot preparations include benzathine penicillin G and methylprednisolone acetate.

- Oral: Enteral drugs may be absorbed in the stomach and small intestine or both. These drugs must be lipid soluble because they must pass through the epithelial cells that line the GI system and then the capillary walls. The rate of absorption may vary widely from one patient to another and from one drug to another depending on a number of drug factors:
    - Lipid solubility.
    - Chemical stability.
    - Environmental pH (gastric and intestinal).
    - Gastric emptying time.
    - Gastrointestinal motility.
    - Presence or absence of food in the stomach.
    - Coadministration of other medications.
    - Coatings on the drug preparation.

  Drugs absorbed through the stomach and intestines (not including the oral mucosa or the rectum) must travel through the portal vein to the liver and undergo extensive first-pass metabolism before they reach systemic circulation. Advantages of oral administration include the ease of administration. Disadvantages include slower absorption, possible nausea and vomiting or gastric irritation, and inactivation of some drugs by digestive acids and enzymes.

  Different types of oral preparations also have different rates of absorption. The following oral preparations are listed from most rapid absorption to least:
    1. Liquids, syrups, and elixirs.
    2. Powders.
    3. Capsules.
    4. Tablets.
    5. Coated tablets.
    6. Enteric-coated tablets.

- Sublingual and buccal: Because of the plentiful blood supply to the mouth, sublingual and buccal medications are rapidly absorbed into the bloodstream and do not undergo first pass metabolism through the liver since they bypass the rest of the GI system. These preparations, such as nitroglycerine, are usually water soluble (hydrophilic/lipophobic) and dissolve readily on contact with saliva.

- Rectal: The absorption can be somewhat unpredictable, especially if stool is present in the rectum, but absorption is usually fairly rapid. This route of administration may be used if the patient is nauseated or cannot tolerate oral medications. While rectal drugs usually are not

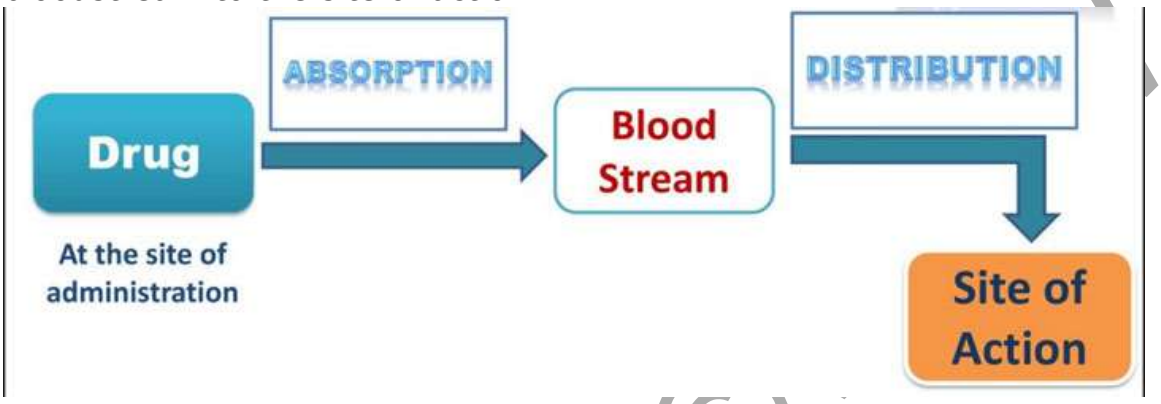
involved in first pass metabolism in the liver, some may be absorbed through the GI system as well as directly into the capillaries present in the rectum.

- Topical: Various preparations include ointment, cream, spray, lotion, and drops. Absorption tends to be local with fewer systemic effects although some is absorbed into the bloodstream. Diclofenac, for example, provides local pain relief but has fewer systemic effects than oral NSAIDs.

- Inhalational: Absorption is very rapid, so effects are often almost immediate. The medication is delivered directly to the lung tissue and into the bloodstream. One disadvantage is that it's easy to overdose because of the rapid absorption, so directions must be followed carefully.

- Transdermal: This is actually one type of topical drug. Transdermal medications tend to be absorbed at a steady rate, such as over a certain number of hours or days; however, the rate of absorption may be affected by perspiration, body temperature, and correct or incorrect application.

Step 2: Distribution: This refers to the transport of a drug through the bloodstream to the site of action.



It's important to remember that most drugs do not bring about positive/therapeutic effects in the blood but must exit the vascular system to reach the actual site of action. This happens at the level of capillaries, where the drugs can pass through the large pores in the capillary walls.

Distribution is determined by the flow of blood as well as the drug's ability to exit the vascular system and to enter cells. Distribution is to the areas with the greatest blood flow first: the heart, liver, kidneys, and brain followed by muscles, skin, and fat.

Drug molecules do not simply float through the blood. Many drug molecules bind to plasma proteins (primarily albumin) and this part of the drug is inactive and cannot exit the vasculature because the protein molecules are too large. The drug molecules that do not bind to proteins are called unbound or free molecules and these are active. The strength of attraction between a drug molecule and albumin varies with different drugs. For example, only 1% of warfarin remains free while 99% of gentamicin remains free.

The level of albumin may affect distribution. If, for example, a burn patient has extensive loss of blood and albumin, then there may be more unbound drug molecules because there are insufficient albumin molecules to bind to, and this could lead to more drug molecules exiting the vascular system and causing a toxic reaction.

If a patient takes two drugs that are highly protein bound, then a **drug-drug reaction** may occur. The drug molecules of both drugs compete for binding sites on albumin molecules, resulting in decreased or increased free drug molecules of the drugs and either increased action or decreased action.

Some drugs do not need to cross a cell membrane because their actions result from binding to receptors on the outside of the membrane.

The capillaries in the central nervous system are different than the capillaries in other parts of the body, resulting in the blood-brain barrier that limits the ability of drug molecules to exit the vasculature. The capillary walls in the CNS have very little space between the cells, so drug molecules cannot pass through these spaces but must be able to pass through the cells themselves. Therefore, in order to reach the CNS, the drug molecules must be lipid soluble (lipophilic/hydrophobic).

Additionally, the P-glycoprotein transporter in the CNS actively pumps drug molecules back into the blood, limiting access. The blood-brain barrier is less active in newborns, so their CNS is more sensitive to drugs.

The barrier between the blood and the placenta is not complete. Drugs that are lipid soluble and nonionized readily pass through the barrier, but drug molecules that are protein-bound do not.

Step 3: Metabolism
Metabolism is the biochemical process (biotransformation) by which the body alters drugs either with or without the action of enzymes. Most drugs are hydrophobic (lipophilic) and convert to a metabolite that is hydrophilic in order to facilitate its elimination.

Metabolism may result in active metabolites or inactive metabolites. Active metabolites have the same pharmacological activity as the original drug but inactive metabolites have none of the pharmacological activity of the original. For example, procaine breaks down into two metabolites that have no anesthetic properties. Some metabolites may be toxic.

In some cases, the drug has no pharmacological action, but its metabolites do. This process is referred to as bioactivation and the drug is referred to as a **prodrug**. An example of this is enalapril, which must be metabolized before it has antihypertensive properties. In some cases, bioactivation of a drug can result in formation of toxic metabolites. Metabolism may result in drugs that are more or less toxic.

The highest concentration of drug digesting enzymes is found in the liver. **Metabolic pathways** include:

- Phase I: Functionalization reactions occur that adds or reveals functional groups (-OH, -SH, -NH2) through oxidation, reduction, or hydrolysis (the process by which a metabolite becomes more hydrophilic or water soluble), resulting in increased polarity of the drug, which facilitates urinary excretion. This process activates or inactivates the parent drug.

  The most common phase I reaction is oxidation. Most oxidation reactions are brought about by a group of oxidases known as (cytochrome P450 (CYT-P450 or P-450). These oxidases are found in high concentration in the liver.

- Phase II: These reactions are referred to as conjugation reactions because they add a functional group to the drug to increase its polarity, making it more water soluble so the drug can be excreted in the urine. The enzyme needed for this reaction is transferase, which transfers the large polar molecules (co-factor) onto the drug.

For example, the most common phase II reaction is glucuronidation, which is done by glucuronosyltransferase. This enzyme uses UDP-GA as a co-factor to transfer glucuronic acid to several functional groups. Glucuronic acid increases the hydrophilic properties of the drug molecule.

The **rate of metabolism** may be affected by a number of factors:

- Patient's age: Newborns have limited drug-metabolizing capacity because the liver doesn't have full ability to metabolize drugs during the first year. Older adults often have decreased enzymatic activity, interfering with their ability to metabolize drugs.

- Induction: Some drugs stimulate the liver to produce more enzymes and thus increase its ability to metabolize drugs. This may increase the rate of metabolism of the stimulating drug and other drugs as well, requiring that the dosage be increased.

- First-pass: Drugs absorbed through the GI system have a first-pass through the liver, and in some cases this process inactivates all or most of the drug. This is the reason that some drugs must be administered parenterally.

- Nutrition: Co-factors needed to facilitate the action of enzymes may be deficient.

- Drug-drug reactions: If more than one drug is metabolized through the same pathway, they may compete, resulting in slowed metabolism of the drugs and the potential for toxic levels to develop.

Grapefruit can inhibit the metabolism of some drugs, resulting in an increase in the blood levels of the drugs. Grapefruit does this by inhibiting CYP-3a4, which is an isoenzyme of CYT-P450, which is found in the liver and the walls of the intestine. Grapefruit primarily inhibits CYP-3a4 found in the intestinal walls, so metabolism of drugs in the intestines is decreased, leaving more drug available for absorption and increasing blood levels.

Many drugs can be affected, including calcium channel blockers, statins, amiodarone, caffeine, carbamazepine, buspirone, triazolam, midazolam, cyclosporine, sirolimus, tacrolimus, SSRIs, dextromethorphan, and sildenafil.

Step 4: Excretion
The kidney is the most important organ of excretion, but the liver and intestines also have roles. Drugs and their metabolites are primarily excreted through the kidneys in the urine, but some excretion also occurs in bile, sweat, saliva, exhaled air, and breast milk.

Most drugs are metabolized in the liver, so by the time they reach the kidneys, little or no original drug compound is present. Because the liver through biotransformation makes the drug metabolites more polar and hydrophilic, they can easily be excreted in the urine.

Biliary excretion also occurs with some fat-soluble drugs. These drugs are released into the bile by the liver and either eliminated in the stool or reabsorbed back into the bloodstream (enterohepatic circulation), so these drugs tend to remain in the body for longer periods of time that water-soluble drugs.

EXCRETION PATHWAYS, TRANSPORT MECHANISMS & DRUG EXCRETED.

Excretory route	Mechanism	Drug Excreted
Urine	GF/ ATS/ ATR, PTR	Free, hydrophilic, unchanged drugs/ metabolites of MW< 300
Bile	Active secretion	Hydrophilic, unchanged drugs/ metabolites/ conjugates of MW >500
Lung	Passive diffusion	Gaseous &volatile, blood & tissue insoluble drugs
saliva	Passive diffusion Active transport	Free, unionized, lipophilic drugs. Some polar drugs
Milk	Passive diffusion	Free, unionized, lipophilic drugs (basic)
Sweat	Passive diffusion	Free, unionized lipophilic drugs
Intestine	Passive diffusion	Water soluble. Ionized drugs

Note: MW refers to molecular weight

The three **processes** by which drugs are excreted in urine include:

- Glomerular filtration: Drugs move from the blood to the urine although protein-bound drugs are too large and are not filtered.

- Active/Passive tubular reabsorption: Lipid-soluble drugs are reabsorbed back into the blood and water-soluble drugs remain in the urine.
- Active tubular secretion: Each drug has its own maximum rate of secretion.

Pharmacokinetic factors
Half-life: The time required for one-half of the drug to be eliminated from the body. The half-life of drugs may vary considerably.

Onset: The time needed after administration for a drug to provide therapeutic effect.

Peak: This is the time at which the drug achieves maximal therapeutic effect. May also refer to the time of the greatest concentration of a drug.

Trough: The time at which the drug has minimal therapeutic response. May also refer to the least concentration of a drug.

Duration of action: The time period during which the level of the drug in the body is sufficient to bring about a therapeutic response without further dosing.

Plasma drug levels: A drug plateau occurs when a drug reaches a steady state and then the dosage of drug eliminated equals the dosage administered. This occurs when a second dose is administered when the half-life (50%) of the first dose occurs and so on until a certain dosage is achieved in the body. If the same dosage of a drug is administered, generally plateau is reached after 4 doses.

Drug monitoring: Peak and trough levels are obtained from blood samples to determine or verify whether the blood level is adequate, too high (toxic), or to low.

Pharmacodynamics:

Pharmacodynamics refers to the biochemical and physical effects of drugs and the mechanisms by which effects are achieved.

Drug mechanisms

Drugs bring about therapeutic response through 3 different mechanisms:

- Receptor interactions: Drug molecules bind to receptor sites. The stronger the bond, the greater the affinity. Those with the greatest affinity achieves the greatest response. Drug molecules may bind in different ways, either as agonists, which bring about a response, or as antagonists, which prevents the binding of agonists or inactivates agonists. Intrinsic activity refers to the drugs ability to activate a receptor after binding with it. Some drugs have high intrinsic activity and others low.

  Agonists bind to receptors and mimic the actions of intrinsic regulatory molecules. Examples of drugs that produce effects by functioning as agonists include insulin, dobutamine, morphine, oxycodone, and methadone.

  Antagonists, on the other hand, bind to receptors and prevent activation of the receptors. Antagonists only have effects if an agonist is present. For example, if a patient has taken an overdose of heroin (an agonist), naloxone (an antagonist) will prevent the agonist from attaching to receptors. However, if the patient did not take the agonist, the antagonist will have no effect.

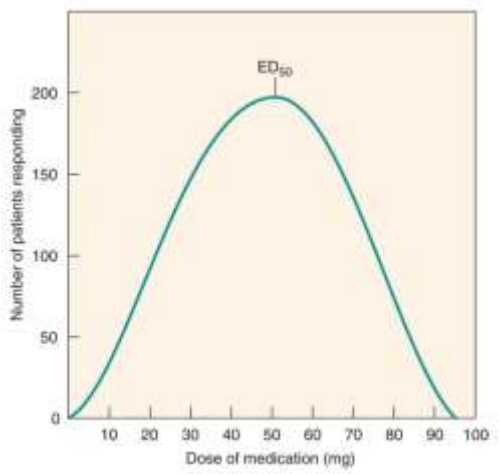
  Partial or non-selective agonists may act as both agonists and antagonists but the effects are less than those of an agonist or antagonist. Examples of a partial agonists are pentazocine and buprenorphine. Buprenorphine activates opioid receptors but the effect is less pronounced than with agonist opioids, so buprenorphine can be used to help wean patients off of other drugs.

- Enzyme interactions: The drug molecules bind with enzyme molecule and inhibits or enhances the enzymes reaction with target molecules.

- Nonselective interactions: These drug molecules do not bind with receptors or enzymes but rather target cell membranes or cellular processes.

Additional factors

Frequency distribution curve: The same drug may not have the same effect or results for every patient. When drugs are developed, studies are carried out to determine the frequency distribution curve, an illustration of how patients respond to the drug at different doses.

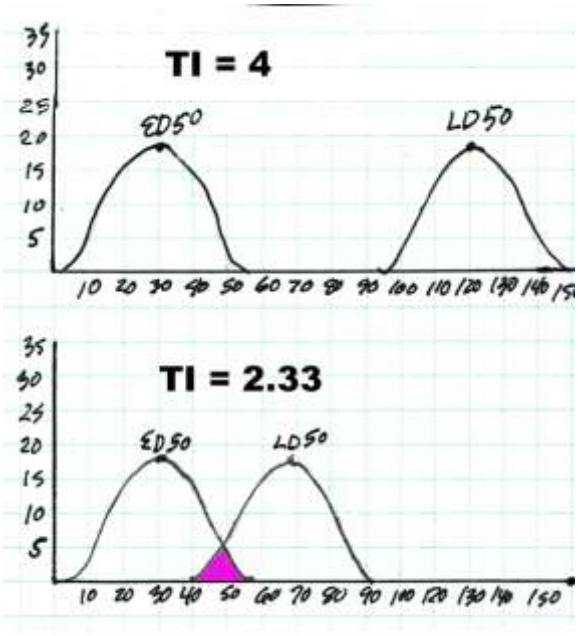


The aim is to determine the dosage that is most effective for the greatest number of patients. The middle of the curve, the dosage at which 50% of the participants had a therapeutic response is the ED_{50} point. This generally becomes the standard dosage and is often the dosage used for initial administration.

However, at this ED_{50} dosage, some patients will have an adequate response and others will not, so dosage often has to be adjusted up or down for the individual patient. A healthcare provider may also choose to start initial dosing at a higher or lower level. In all cases, any time a patient starts a new drug, the patient must be carefully monitored for response.

Therapeutic index: The therapeutic index of a drug is the measure of the drug's safety. The therapeutic index is based on animal studies and represents the ratio of the drug's LD_{50} (the dose that is lethal to 50%) to its ED_{50}:

- LD_{50}/ED_{50} = TI.
- For example, if the ED_{50} is 20 mg and the LD_{50} is 200 mg, the therapeutic index is 10, meaning that a lethal dose would need to be 10 times the therapeutic dose. 200/20 = 10

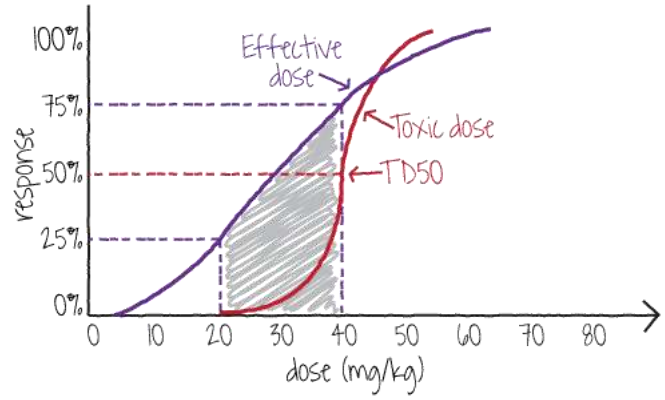


Note in the adjacent therapeutic index curves that the curves in the upper example do not overlap and the TI is 4, meaning a lethal dose is 4 times the therapeutic dose.

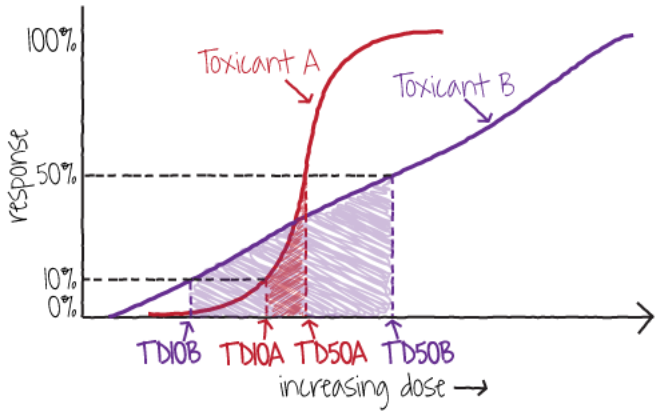
In the second example, there is an overlap between the two curves and the TI is only 2.33. The therapeutic dose is 30, but the curve for the lethal dose begins at 40 and peaks at 70mg, making this drug more dangerous to give than the first drug because there is little room for error or personal variations in response.

Additionally, according to the second example, because some people require a high dose up to about 55 mg to achieve therapeutic results, there is a risk that the drug might cause death at therapeutic levels. To be safe, a drug must have the highest dose that produces therapeutic results considerably lower than the lowest drug to produce lethal results.

Margin of safety: Because the therapeutic index can sometimes be misleading about the safety of drugs, the margin of safety must also be considered. The margin of safety is defined as the ratio of the toxic dose to 1% of the population (TD_{01}) to the effective dose to 99% of the population (ED_{99}).



Note in this comparison of effective doses and toxic doses that there is considerable overlap. While larger doses are more effective, there is also a greater chance of producing toxicity, so lower doses are safer.



Some drugs may exhibit a sharp increase in toxic effects with small increases in dosages (toxicant A) while others may require a larger increase in dosage to increase toxic effect (toxicant B).

Research studies identify the highest dose at which NO toxic effects occur and the lowest does at which toxic effects do occur:

- NOAEL or NOEL: Highest dose at which no toxic or adverse effects observed.
- LOAEL or LOEL: Lowest dose at which toxic or adverse effects observed.

Conclusion:

When treating patients, the primary consideration is the safety and well-being of the patient. While herbs have been used for treatment of disease for many years, in modern times, many thousands of drugs have been synthesized, leading at times to seemingly miraculous cures.

However, drugs are not without problems. Overuse of antibiotics has resulted in increased resistance to drugs, and some drugs have proven over time to have adverse effects that were not anticipated or discovered in initial research and clinical trials.

The healthcare provider must have a thorough understanding of pharmacotherapeutics and the ways in which pharmacokinetics and pharmacodynamics correlate with treatment and disease and how drugs can interact with each other.

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