Introduction to Pharmacology| Pharmacy Notes

Pharmacy Notes

Pharmacology *(Gr. pharmakon – a drug or poison, logos – word or discourse)* is the science dealing with actions of drugs on the body (pharmacodynamics) and the fate of drugs in the body (pharmacokinetics). It overlaps with pharmacy, the science of preparation of drugs; much of it deals with therapeutics, the treatment of disease (by whatever means).

Toxicology is the branch of pharmacology dealing with the "undesirable" effects of drugs on biological processes (in the case of a nerve gas the bad effect may be a desired one).

In order for a drug to work, it must enter the body and somehow be distributed in such a way that it gets to its site of action. In most cases the site of action is a macromolecular "receptor" located in the target tissue. Most drug effects are temporary, because the body has systems for drug detoxification and elimination. We will consider these issues broadly for now and go into more depth in individual lectures. As you read, refer to the figure below:

Overview of Pharmacokinetics: -

> *Pharmacokinetics: - "What the body does to the drug"*

1. The drug may enter the body in a variety of ways: as an oral liquid, pill, or capsule; as an inhaled vapor or aerosol; absorbed through intact skin or a mucous membrane; injected into muscle, subcutaneous tissue, spinal fluid, or directly into the bloodstream. As we shall see, the physical properties of the drug and the specific way it is prepared greatly influence the speed of absorption.

2. If the drug is given orally and swallowed, it must be absorbed from the GI tract into the portal circulation. If it is absorbed from the skin, mouth, lungs or muscle it will go directly into the systemic circulation. If drug is injected directly into the bloodstream (e.g., intravenous injection), 100% of it is available for distribution to tissues. This is not usually the case for other modes of administration. For example, drug which is absorbed via the portal circulation must first pass through the liver which is the primary site of drug metabolism (biotransformation). Some of the drug may therefore be metabolized before it ever reaches the systemic blood. In this case, "first-pass" metabolism reduces the bioavailability to less than 100%.

3. Once the drug is in the bloodstream a portion of it may exist as free drug, dissolved in plasma water. Some drug will be reversibly taken up by red cells and some will be reversibly bound to plasma proteins. For many drugs, the bound forms can account for 95-98% of the total. This is important because it is the free drug which traverses cell membranes and produces the effect. It is also important because protein-bound drug can act as a reservoir which releases drug slowly and thus prolongs its action.

4. The unbound drug may then follow its concentration gradient and distribute into peripheral tissues. In some cases, the tissue contains the target site and in others the tissue is not affected by the drug. Sites of non-specific binding act as further reservoirs for the drug. This total volume of distribution determines the equilibrium concentration of drug after a specified dose.

5. Tissue-bound drug eventually reenters the bloodstream where it perfuses the liver and kidneys. The liver metabolizes most drugs into inactive or less active compounds which are more readily excreted. These metabolites and some of the parent compound may be excreted in the bile and eventually may pass out of the body in the feces. Alternatively, some of the drug may be reabsorbed again, farther down the GI tract (the so-called enterohepatic cycle). Any biotransformed drug which is not excreted in bile passes back into the systemic circulation.

6. Parent drug and metabolites in the bloodstream may then be excreted: most are filtered by the kidney, where a portion undergoes reabsorption, and the remainder is excreted in the urine. Some drugs are actively secreted into the renal tubule. Another route of excretion is the lung: Drugs like alcohol and the anesthetic gases are eliminated by this route. Smaller amounts of drug are eliminated in the sweat, tears and breast milk.

7. Biotransformation may sometimes produce metabolites with a great deal of activity. Occasionally, we administer a parent drug whi
inactive (a pro-drug) and only the metabolite has activity.

Overview of Pharmacodynamics

> *Pharmacodynamics – "What the drug does to the body"*

As stated above, the majority of drugs bind to specific receptors on the surface or interior of cells, but there are many other cellular components and non-specific sites which can serve as sites of drug action.

1. Water can be a target. Osmotic diuretics like mannitol are not reabsorbed by the kidney, and the osmotic load they create in the renal tubule obligates the loss of water. Laxatives like magnesium sulfate work in the intestine by the same principle.

2. Hydrogen ions can be targets. Ammonium chloride is sometimes used to acidify the urine. When it is taken orally, the liver metabolizes ammonium ion to urea, while the chloride is excreted in the urine. The loss of Cl- obligates the loss of H+ in the urine, thus the pH is lowered.

3. Metal ions can be targets. Chelating agents like EDTA may be used to bind divalent cations like Pb++. Metal ions are most frequently drug targets in cases of poisoning.

4. Enzymes are targets of many therapeutically useful drugs. Drugs may inhibit enzymes by competitive, non-competitive, or irreversible blockade at a substrate or cofactor binding site. Digitalis glycosides increase myocardial contractility by inhibiting the membrane enzyme, Na+-K+ – ATPase. Antimicrobial and antineoplastic drugs commonly work by inhibiting enzymes which are critical to the functioning of the cell. In order to be effective, these drugs must have at least someselective toxicity toward bacterial or tumor cells. This usually means that there is a unique metabolic pathway in these cells or some difference in enzyme selectivity for a common metabolic pathway. An example of this is the inhibition of folate synthesis by sulfonamides. These drugs are effective antibacterial agents because the bacteria depend upon folate synthesis, while the host doesn't. This example will be covered in detail in one of our case discussions.

5. Nucleic acids are targets for antimetabolites and some antibiotics. In the case of 5- fluorouracil, the compound acts as a counterfeit substitute for uracil and becomes incorporated into a faulty mRNA. Antisense oligonucleotides are another very specific way to interfere with a restricted part of the genome.

6. Some drugs, like general anesthetics, appear to act by non-specific binding to a macromolecular receptor target. These drugs are thought to alter the function of membrane proteins, in part, by disordering the structure of the surrounding lipid membranes. Their lack of specificity is reflected in very low chemical structural requirements. The general anesthetics include compounds as chemically diverse as nitrogen, xenon, halogenated ethers, and steroids. They exhibit very little stereoselectivity, that is, there are not marked differences in anesthetic activity between enantiomers.
