Introduction to Chemotherapy and Chemotherapeutics

Drug therapy is divided into two major categories depending on the therapeutic intent:

CHEMOTHERAPY: Chemotherapy refers to the use of drugs to kill or inhibit the growth of foreign organisms in the patient. Cancer cells are included as foreign organisms along with bacteria, fungi, viruses, protozoans, and metazoans.

PHARMACOTHERAPY: Pharmacotherapy refers to the use of drugs to alter the rate of reactions or processes characteristic of the host itself.

Given these distinctions, it is apparent that the action of chemotherapeutic agents should be highly specific for the foreign cell with minimal effect on the host. In contrast, a pharmacotherapeutic agent must have activity on the host.

For both chemotherapy and pharmacotherapy the desire is to achieve SPECIFICITY (SELECTIVITY) in the drug's action, that is to produce the desired action with no adverse effects on the host. Because all drugs produce adverse effects at some dose, the ratio of doses required to produce the various effects is an important indicator or specificity. The concept of specificity may be illustrated by noting that the dose response curve for a highly specific drug is far to the left (i.e., a much lower dose is required) of the curve for the most significant adverse reaction.

How do drugs work?

Our bodies are largely controlled by proteins. Proteins exist in many different forms in the body and have many different functions. Each protein has a specific function and is quite specific to the cell type that it acts on. For example, there are specific types of proteins called receptors. Receptors are embedded on the cell surfaces, there are different receptors for different types of cells. A liver cell will have different receptors than a cardiac cell. The receptor binds to other proteins and chemicals on the outside of the cell and this in turn creates a change in the functioning of the cell.

Proteins also act as drug targets. In order for a drug to exert an effect it needs to be bound to a protein. This can be thought of as a lock and key system; where the drugs are the key and the protein is the lock. Once the drug is bound in this lock and key mechanism it can have one of

two main influences over the cell. It can produce a change in response or it can stop a normal response of the cell.

Drugs that produce a change in the cell functioning are called agonists. Drugs that stop a normal function of the cell are called antagonists.

Pharmacodynamics: What do drugs do to the body?

Once the drug is bound to a protein it exerts a **therapeutic effect** on the body, this is the pharmacodynamics of a drug. There is an enormous list of different drugs and their actions in the body. Below are links to just some of the major treatment areas.

- Cancer
- Contraception
- Pain
- Respiratory
- Obesity
- Infection

Pharmacokinetics: what happens to drugs in the body?

Pharmacokinetics is the study of what happens to drugs once they enter the body. The main stages include:

- The absorption of the drug into the blood and across cell membranes to enter the cells;
- The distribution of the drug throughout the body;
- The metabolism or breakdown of the drug; and
- The excretion of the drug from the body.

Each drug will have a unique bioavailability. This is the amount of drug *available* to have an effect on the biological system. A drug's bioavailability is determined by its pharmacokinetics. For example, some drugs are poorly absorbed as they do not cross cell membranes as quickly or as effectively as others and so less of the drug will pass into the systemic circulation where it needs to be in order to have an effect.

The proportion of the drug that does pass into the circulation is called the drug-plasma concentration. When a drug is absorbed into the circulation, the plasma concentration will increase until it reaches a peak and then as the drug is metabolised this plasma concentration will decline until the entire drug has been metabolised and then excreted from the body.

Depending on the characteristics of the drug some will reach the peak plasma concentration quicker than others or be metabolised faster and so on.

Each drug has a range of dosages that can effectively treat a condition while still remaining safe. That is, the range between the lowest dose that has a positive effect, and the highest dose before the negative effects outweigh the positive effects. This is known as the *therapeutic window* the drug. This can vary substantially between different types of drugs. For example, one drug could be safe and efficacious anywhere between 5mg to 20mg of whereas another could have the therapeutic window between 15mg and 20mg.

Why do the effects of drugs vary between different people?

Many of the reasons that we see such a wide and diverse range of efficacies of drugs across people are that drugs work differently in different people. A drug will usually produce the same qualitative effect across individuals, that is to say that it will produce the same end result and the same side effects but the quantity of these effects will be different. So some people may experience a shorter action of the drug or a more intense side effect.

This variation is due mostly to differences in pharmacokinetics and pharmacodynamics between ethnicity, age, genetic makeup and disease state.

Ethnicity

There are quite substantial differences in drug metabolism between people of different ethnicities. Asians are usually more sensitive to most drugs than Caucasians and Caucasians are more sensitive then afro-carrabeans.

Age

Elimination of the drug from the body is directly influenced by age. Newborns and elderly experience the effects of drugs for longer and the drug takes a lot longer to be eliminated from the body.

Newborns

When babies are born to term, their renal function is very quick to establish similar levels to adults within one week after birth. If the baby is born prematurely it can take 8 weeks or more

to reach the level of enzymes necessary. If drugs are given before the renal function is at this level, the drug elimination from the body takes a lot longer and so do the effects of the drugs.

Elderly

Renal filtration rate begins to decline at 20 years of age and by 50 years of age it has declined by 50%. This again will affect the elimination of drugs from the body.

Genes

The differences in our genes are also an important determinant of variability in what our bodies to do the drugs.

Disease state

There are many different disease states that affect pharmacokinetics. In fact most diseases will affect pharamcokinetics to some degree and this is for your doctor to determine and consider when prescribing medication. Diseases of the liver and kidneys will affect drug metabolism and excretion whereas diseases of the gastroenterological systems will affect the absorption of drugs. Receptors, the blood-brain barrier, blood, heart and skin are just some other areas that, if affected by disease, can impair the therapeutic action of drugs.

Developing a pharmaceutical product

Developing pharmaceutical products is an extremely expensive and long process, costing billions of dollars and taking over a decade to produce one drug! There are three main stages in the drug development process. These are:

- Laboratory methods: this includes testing the newly formed/discovered molecule on cell cultures(these are cells in dishes in labs not within living organisms) and then animals (usually either rats or mice).
- Clinical trials: firstly on healthy human volunteers then moving onto patients undergoing medical treatment.

- Socioeconomic methods: assessment of the drug in the community, the adverse effects, the family of the patient's response, the healthcare costs etc.

Each stage of the process must pass strict safety and efficacy testing before the medicine can progress. Throughout all stages the scientists are determining the benefits versus risks of the new drug. For every drug there will be side effects and adverse effects in some patients. In order to determine whether the drug will have an overall benefit, the proportion of patients that respond positively to the treatment must be compared to the number of patients that respond negatively. So for example in a clinical trial sample of 1000 patients, if 996 patients experience a significant improvement in quality of life and 4 patients experience an adverse drug reaction, more than likely the benefit outweighs the risk in this case. If 550 patients significantly improve and 450 patients experience adverse drug reactions the drug is not likely to be marketed. This of course depends on the nature and severity of the adverse events.

Once the drug has been determined to be safe, effective and a significant cost-benefit it may be produced, marketed and distributed to the public. In Australia,

Disease Classification:

A disease is a condition of impaired health resulting from a disturbance in the structure or function of the body. Diseases may be classified into the following major categories:

1) **Infections** caused by viruses, ricketsia, bacteria, fungi, protozoa and worms
2) **Allergic diseases** caused by antigens and foreign substances
3) **Metabolic disorders** caused by defects in the body's ability to carry out normal reactions - these may be hereditary, deficiency, and congenital defects
4) **Cance**r
5) **Toxic diseases** caused by poisons
6) **Psychosomatic and mental diseases**

Chemotherapy, broadly defined, means the treatment of any disease by chemicals including infectious and non-infectious diseases. The original definition applied only to drugs which were used in the treatment of infectious diseases. The proper term for the treatment of non-infectious diseases is pharmacodynamics.

Drug action: The function of a drug in various body systems.

Local: When the drug is applied locally or directly to a tissue or organ, it may combine with t he cell's membrane or penetratethe cell. Its action may be (1) astringent when the drug causes the cell or tissue to contract, (2) corrosive when the drug isstrong enough to destroy cells, or (3) irritating when too much of the drug combines with cells and impairs them.

General, or systemic: This type of action occurs when the drug enters the bloodstream by abs orption or direct injection,affecting tissues and organs not near the site of entry. Systemic acti on may be (1) specific, when it cures a certain disease;(2) substitutive or replenishing, when it supplies substances deficient in the body; (3) physical, when some cell constituentsare dissol ved by the action of the drug in the bloodstream; (4) chemical, when the drug or some of its pr inciples combine withthe constituents of cells or organs to form a new chemical combination; (5) active by osmosis, caused by dilution of salt (alsoacids, sugars, and alkalis) in the stomach or intestines by fluid withdrawn from the blood and tissues; or by diffusion, whenwater is abs orbed by cells from the lymph; (6) selective, when action is produced by drugs that affect only certain tissues ororgans; (7) synergistic, when one drug increases the action of another; (8) an tagonistic, when one drug counteracts another;(9) physiological, when the drug exerts a potent ially beneficial effect similar to that which the body normally produces; (10)therapeutic, when the effect is to treat or repair diseased organs or tissues; (11) side active, creating an undesire d effect; (12)empirical, producing results not proved by clinical or laboratory tests to be effect ive; or (13) toxicological, having a toxic orundesired effect, generally the result of overdose o r long-term usage.

Cumulative: Some drugs are slowly excreted or absorbed so that with repeated doses an accu mulation in the body producesa toxic effect. Such drugs should not be administered continuou sly.

Incompatible: Undesired side effects occur when some drugs are administered together. This may be due to the antagonisticaction of one drug on others or to a physical interaction of the drugs that inactivates one of them.

The challenge

Many diseases caused by pathogens (viruses, bacteria, parasites) have developed protein mutations that render them either increasingly or completely resistant to established drug treatments. Standard treatments can also have significant side effects or be ineffective in preventing recurrent infection. There is an urgent need for new treatments that can overcome

existing mutations. Also, new targets must be discovered with features that are less subject to such resistance or able to be more precisely targeted, generating fewer treatment side effects and toxicities.

MECHANİSMS OF ANTİBACTERİAL DRUGS

1. Inhibitors of Cell Wall Biosynthesis :

Several different classes of antibacterials block steps in the biosynthesis of **peptidoglycan**, making cells more susceptible to osmotic lysis. Therefore, antibacterials that target cell wall biosynthesis are bactericidal in their action. Because human cells do not make peptidoglycan, this mode of action is an excellent example of selective toxicity.

2. Inhibitors of Protein Biosynthesis

The cytoplasmic **ribosomes** found in animal cells (80S) are structurally distinct from those found in bacterial cells (70S), making protein biosynthesis a good selective target for antibacterial drugs.

Protein Synthesis Inhibitors That Bind the 30S Subunit

Aminoglycosides are large, highly polar antibacterial drugs that bind to the 30S subunit of bacterial ribosomes, impairing the proofreading ability of the ribosomal complex. This impairment causes mismatches between codons and anticodons, resulting in the production of proteins with incorrect amino acids and shortened proteins that insert into the cytoplasmic membrane. Disruption of the cytoplasmic membrane by the faulty proteins kills the bacterial cells. The **aminoglycosides**, which include drugs such as **streptomycin**, **gentamicin**, **neomycin**, and **kanamycin**, are potent broad-spectrum antibacterials. However, aminoglycosides have been shown to be nephrotoxic (damaging to kidney), neurotoxic (damaging to the nervous system), and ototoxic (damaging to the ear).

Protein Synthesis Inhibitors That Bind the 50S Subunit

There are several classes of antibacterial drugs that work through binding to the 50S subunit of bacterial ribosomes. The macrolide antibacterial drugs have a large, complex ring structure and

are part of a larger class of naturally produced secondary metabolites called **polyketides**, complex compounds produced in a stepwise fashion through the repeated addition of two-carbon units by a mechanism similar to that used for fatty acid synthesis. Macrolides are broad-spectrum, bacteriostatic drugs that block elongation of proteins by inhibiting peptide bond formation between specific combinations of amino acids.

3. Inhibitors of Membrane Function

A small group of antibacterials target the bacterial membrane as their mode of action (Table 4). The **polymyxins** are natural polypeptide antibiotics that were first discovered in 1947 as products of *Bacillus polymyxa*; only polymyxin B and polymyxin E (**colistin**) have been used clinically. They are lipophilic with detergent-like properties and interact with the lipopolysaccharide component of the outer membrane of gram-negative bacteria, ultimately disrupting both their outer and inner membranes and killing the bacterial cells. Unfortunately, the membrane-targeting mechanism is not a **selective toxicity**, and these drugs also target and damage the membrane of cells in the kidney and nervous system when administered systemically.

4. Inhibitors of Nucleic Acid Synthesis

Some antibacterial drugs work by inhibiting nucleic acid synthesis (Table 5). For example, **metronidazole** is a semisynthetic member of the nitroimidazole family that is also an antiprotozoan. It interferes with DNA replication in target cells. The drug **rifampin** is a semisynthetic member of the **rifamycin** family and functions by blocking RNA polymerase activity in bacteria. The RNA polymerase enzymes in bacteria are structurally different from those in eukaryotes, providing for **selective toxicity** against bacterial cells.

5. Inhibitors of Metabolic Pathways

Some synthetic drugs control bacterial infections by functioning as **antimetabolites**, competitive inhibitors for bacterial metabolic enzymes (Table 6). The **sulfonamides** (**sulfa drugs**) are the oldest synthetic antibacterial agents and are structural analogues of *para*-aminobenzoic acid (PABA), an early intermediate in folic acid synthesis

6. Inhibitor of ATP Synthase

Bedaquiline, representing the synthetic antibacterial class of compounds called the **diarylquinolones**, uses a novel mode of action that specifically inhibits mycobacterial growth. Although the specific mechanism has yet to be elucidated, this compound appears to interfere with the function of **ATP** synthases, perhaps by interfering with the use of the hydrogen ion gradient for ATP synthesis by **oxidative phosphorylation**, leading to reduced ATP production.

DRUG RESISTANCE

The emergence of drug resistance severely limits the arsenal of available drugs against protozoal pathogens. Parasites have evolved numerous ways to overcome the toxicity of drugs (Box). Quite often drug resistance involves mutations in the drug target so that the drug does not bind or inhibit the target as well. Drug resistance can develop quickly in situations where a single point mutation can confer resistance. Another mechanism of drug resistance involves expressing higher levels of the target. This can be accomplished either through increased transcription and translation or gene amplification. This results in a requirement for higher levels of drugs to achieve the same level of inhibition. Decreasing drug accumulation or metabolizing the drug to non-toxic products will result in less drug reaching the target and can also contribute to drug resistance. Drug resistance can also involve the accumulation of mutations in the same or different targets which will have additive or synergistic effects. Parasites with mutations or genetic polymorphisms which confer a decrease in drug sensitivity will be selected under drug pressure.

Different antibiotics have different modes of action, owing to the nature of their structure and degree of affinity to certain target sites within bacterial cells.

1. **Inhibitors of cell wall synthesis**. While the cells of humans and animals do not have cell walls, this structure is critical for the life and survival of bacterial species. A drug that targets cell walls can therefore selectively kill or inhibit bacterial organisms. Examples: penicllins, cephalosporins, bacitracin and vancomycin.
2. **Inhibitors of cell membrane function**. Cell membranes are important barriers that segregate and regulate the intra- and extracellular flow of substances. A disruption or damage to this structure could result in leakage of important solutes essential for the cell's survival. Because this structure is found in both eukaryotic and prokaryotic cells, the action of this class of antibiotic are often poorly selective and can often be toxic for

systemic use in the mammalian host. Most clinical usage is therefore limited to topical applications. Examples: polymixin B and colistin.

3. **Inhibitors of protein synthesis**. Enzymes and cellular structures are primarily made of proteins. Protein synthesis is an essential process necessary for the multiplication and survival of all bacterial cells. Several types of antibacterial agents target bacterial protein synthesis by binding to either the 30S or 50S subunits of the intracellular ribosomes. This activity then results in the disruption of the normal cellular metabolism of the bacteria, and consequently leads to the death of the organism or the inhibition of its growth and multiplication. Examples: Aminoglycosides, macrolides, lincosamides, streptogramins, chloramphenicol, tetracyclines.
4. **Inhibitors of nucleic acid synthesis**. DNA and RNA are keys to the replication of all living forms, including bacteria. Some antibiotics work by binding to components involved in the process of DNA or RNA synthesis, which causes interference of the normal cellular processes which will ultimately compromise bacterial multiplication and survival. Examples: quinolones, metronidazole, and rifampin.
5. **Inhibitors of other metabolic processes**. Other antibiotics act on selected cellular processes essential for the survival of the bacterial pathogens. For example, both sulfonamides and trimethoprim disrupt the folic acid pathway, which is a necessary step for bacteria to produce precursors important for DNA synthesis. Sulfonamides target and bind to dihydropteroate synthase, trimethophrim inhibit dihydrofolate reductase; both of these enzymes are essential for the production of folic acid, a vitamin synthesized by bacteria, but not humans.