

Concepts of pharmacodynamics



**ASSIGN
BUSTER**

1a) Pharmacodynamics can be defined as the study of a drug what it does to a body, whereas Pharmacokinetics means a study of a body response to a drug. Pharmacodynamics sometimes abbreviated as “ PD”, Pharmacokinetics as “ PK” and in conjunction of both can be referred to as “ PKPD”.

In upcoming years substantial efforts were devoted to systematically elucidate the dynamic relationship between pharmacokinetic and pharmacodynamic variables. The main concept of this pharmacokinetic pharmacodynamic approach is to use the concentration effect relationship between the drug and the dosage alteration and growth of product in a valid way to minimize trial and error approaches. This approach can potentially result in considerable savings of time and expenses and use to avoid unnecessary and unethical clinical studies. Thus, the dosages and dosing intervals of agents like antimicrobial should be intended with orientation to active pharmacokinetic and pharmacodynamic parameters. According to the several effectiveness indices or replacement markers that taken into account for both pharmacokinetic and pharmacodynamic information have been defined and used to describe the antibacterial activity of various classes of antimicrobial agents.

b)

The Agonist workings with the muscles and the antagonist are the muscle functioning against it in a contraction. That is Bicep curl, the agonist is the Biceps brachia and the antagonist muscle is the triceps brachia. The word agonist means “ producing an action”, an antagonist opposes that action. Agonist binds to a receptor site and results to a response in drug,

often imitating the natural body reaction, and antagonist acts against this and blocks the response. Both are polypeptide hormones, which specific act at the intensity of the hypothalamus and pituitary to affect the secretion of gonadotropins from specific cells in the pituitary.

A mixture of these results to a drug or receptor called ligand which possesses properties which is alike to both AGONISTS and ANTAGONISTS for certain RECEPTOR sites. Well known mixed drug of these that work together with OPIOID (morphine-like) receptors. For example, in Parkinson disease, drug levodopa is used. The long use of this drug can cause uncontrollable, rough body movements called dyskinesias which are inhibit a person's ability to function. Pentazocine, nalbuphine, butorphanol, and BUPRENORPHINE are all mixed agonist-antagonists for opioid receptors. Dopamine agonists mimic the property of dopamine in the brain by exciting dopamine acceptors with a lower risk of the uncontrollable and irreversible dyskinesias that is associated with levodopa therapy.

c)

After the drug enters the circulation, it is distributed into the body tissues. The distribution of drug is usually irregular because of differences in blood perfusion, tissue binding, regional pH, and the permeability of cell membranes. The rate at which the drug enters into a tissue depends on the blood flowing to the tissue, tissue mass, and partition character between blood and tissue. When the tissues are in distribution equilibrium i. e when the entry and exit rates are the same between blood and tissue is reached the drug move rapidly in richly vascularized areas, diffusion across cell

membranes is the rate limiting step. In that case it is a need, drugs should be soluble in lipids as they are helpful in effective transportation. As one of the fundamental unit is lipid. These non-polar solvents are themselves lipophilic. Lipophilic substances interact within themselves and with other substances through the London dispersion force. Drug permeation occurs largely in the capillary bed, where both surface area and time available for exchange are maximal. Sometimes it gets effected by extensive vascular branching, low velocity of flow. Drugs rapidly cross capillary membranes into tissues because of passive diffusion and hydrostatic pressure. It is mostly determined as capillary structure or chemical properties of drugs.

3)

Oral drug delivery is the most advantageous and preferred technique of administering therapeutic agents for their general effects. The oral medication is generally considered as the first path investigated in the detection and growth of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience in administration, and cost-effective manufacturing process. The drug substances, conservative instant discharge formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patient. The bioavailability of the drugs can be determined by their formulation, which means that the rate at which they can dissolve in the gastrointestinal tract in the body.

Bioavailability shows the difference between the amounts of a matter, such as a drug, herb, or chemical, on to which a person is exposed and the

original amount that the body receives. Bioavailability denotes the dissimilarity between exposure and dose. A drug's remedial action or toxicity is resolute by the dose received at the objective site in the body. The dose received by the target site is formulated by the quantity of the substance absorbed by the body, which depends on its bioavailability. If a substance is ingested, its bioavailability is determined by the amount that is immersed by the intestinal tract in the body. And when the substance is inhaled then the bioavailability is resolute by the amount that is absorbed by the lungs in the body. Bioavailability is serious to formative the quantity of a drug to administer or the level of chemical exposure that is likely to create toxicity.

The oral route offers an attractive approach of drug targeting at the specific sites within GI tract for the treatment of certain pathological conditions, such as gastroesophageal reflux disorder, gastroduodenal ulcers, inflammatory bowel disease, and stomach and colon cancers. Oral drug delivery systems having three categories: immediate release preparations, controlled release preparations, and targeted release preparations. Calcium is more easily absorbed by the gastrointestinal tract in the body than calcium carbonate so the bioavailability of calcium is more in the body.

4. Drug metabolism is the biochemical change of pharmaceutical substance by living organisms, usually through focused enzymatic systems. This is a form of xenobiotic metabolism. Drug metabolism often converts lipophilic substance compounds into more readily excreted polar products. Its rate is an important determinant of the duration and intensity of the pharmacological action of drugs.

Drug metabolism can result in toxication or detoxication – the activation or deactivation of the chemical. While both occur, the major metabolites of most drugs are detoxication products. Drugs are almost all xenobiotics. Other commonly used organic chemicals are also xenobiotics, and are metabolized by the same enzymes as drugs. This provides the opportunity for drug-drug and drug-chemical interactions or reactions.

Paracetamol is metabolized primarily in the liver, into non toxic products. Three metabolic pathways are notable: Glucuronidation is supposed to account for forty percentages to two thirds of the metabolism of paracetamol. Sulfation sulfate conjugation may account for twenty to forty percent in the metabolism.

N hydroxylation and reorganization, then Glucuronidation conjugation, accounts for less than fifteen percent. The hepatic cytochrome enzyme system metabolizes paracetamol, forming a small and significant alkylating metabolite known as N acetyl p benzo quinone imine, and it is then irreversibly conjugated with the sulfhydryl groups of glutathione.

Every pathways give way final products that are inactive, non toxic, and eventually excreted by the kidneys. The intermediate product NAPQI is toxic. NAPQI is principally responsible for the toxic effects of paracetamol, and this is an example of toxication. Production of N Acetyl P Quinone Imine is mostly due to two isoenzymes of cytochrome. The gene is extremely polymorphic and differences in paracetamol toxicity are supposed to be due to isoenzyme. Heritable polymorphisms may contribute significantly at different rates of production of N Acetyl P Quinone Imine. It can be classified as

extensive, ultra rapid and poor metabolizers produce by NAPQI, depending on their levels of expression. Although metabolises paracetamol into N Acetyl P Quinone Imine to a lesser level than other enzymes, its action may contribute to paracetamol toxicity in extensive and ultra rapid metabolisers when paracetamol is taken at very large doses. While taking as usual doses the NAPQI is quickly detoxified by conjugation. The overdose of paracetamol is in extensive and ultra rapid metabolizers, this detoxification pathway becomes saturated and consequently N Acetyl P Quinone Imine accumulates.

5. In silico is a method which helps in identifying targets of drugs via bioinformatics tools. In silico method can also be used to examine the target structures for possible sites of binding, and it is used to generate candidate molecules, this method check for their drug similarity, and tie these molecules with the target molecules, and order them according to their binding affinities, and improve binding characteristics of the molecules.

By using the computers and computational methods for all aspects of drug discovery and due to this it forms the center of composition based drug design. The computers contains a great level of performance in computing, data management software and internet aid in accessing of huge amount of data generated and transforming the enormous composite biological data into practical knowledge in current drug discovery process. The use of corresponding investigational and informatics techniques increases the possibility of success in many phases of the drug discovery process, from the classification of work of novel targets and exposition of their functions to the finding and development of lead compounds with preferred properties.

Computational tools propose the benefit of delivering new drug candidates rapidly and at a lower cost.

The roles of computation in discovery of drug are;

1. Effective screening & de novo design,
2. in silico ADME/T prediction and
3. Advancement in the methods for determining protein-ligand binding

6. Microdosing is a technique for understanding the behavior of drugs on human body through the insertion of doses as low as they are improbable to produce effects on whole body, but sufficient enough to permit the cellular response to be considered. Pharmacokinetics is the drug with almost no risk of side effects on the human body. This is termed as Phase 0 of study and it is frequently conducted before medical Phase I to estimate whether a drug is feasible for the next phase of testing. Human Microdosing aims to decrease the resources used up on non practical drugs and the quantity of testing performed on animals. The basic step is to tag an entrant drug using the radioisotope carbon 14 dating and then manage the complex to human volunteers at different levels in general about several times lower than the proposed therapeutic dosage, and check how the body responds for example its exchange of the original drug into other molecules, and how long they stay in the body. The amount of radioactivity administered is classically around two hundred nano Curies, which is low as to be considered ' non-radioactive' by authorities

Advantages

Microdosing offers a faster and potentially less expensive approach to obtaining human in vivo PK data in early clinical drug development.

It encompasses the use of pharmacologically inactive doses of test drug in the low microgram range along with ultrasensitive assay methods (PET, AMS) to assess human exposure in order to extrapolate the PK of higher, clinically more relevant doses, assuming linear PK.

Disadvantages

Questions regarding the accuracy of micro dosing have to be answered and there is no sufficient studies to clearly demonstrate whether the body's reaction to a specific compound is related or similar, when used as micro dose and in its pharmacological dose; it could lead to fake negatives or fake positives compound suitable based on micro dose data but discarded consequently when used in pharmacological doses.

7 a)

Atenolol is a blocking agent which blocks the effects of drugs, for eg, adrenaline or epinephrine, on nerves of the nervous system. It is used to stimulate the heart to beat more quickly. By blocking the stimulation of these nerves, it reduces the heart rate and is helpful in treating unusually rapid heart rhythms. It decreases the force of reduction of heart muscle and it the lowers blood pressure. Decrease the heart rate, the strength of muscle contraction, and the blood pressure beside which the heart must pump, it slows down the work of the heart muscle and the need of the muscle for

oxygen. When oxygen necessarily of the heart muscle exceeds the supply because of this angina occurs, it is helpful in treating angina.

Atenolol is prescribed for patients with high blood pressure. It is also used to take care of chest pain related to coronary artery disease. It is helpful in slowing and adaptable convinced types of strangely rapid heart rates it is also prescribed for acute heart attack. . This drug works by blocking the action of certain usual chemicals in body such as epinephrine on the heart and blood vessels. These results in a lowering of the heart rate, blood pressure, and strain on the heart.

Doses of Atenolol for better use should be taken before meals and before bedtime. The dose should be taken for treating high blood pressure is small mg once daily. It is typically well tolerated, and side effects are mild and temporary. Side effects include slow heart rate, low blood pressure. The patients with slow heart rates and heart blocks, it can cause dangerously slow heart rates, and even shock, because it reduces the force of contraction between the heart muscles and can exacerbate symptoms of heart failure. Patients with coronary artery disease, suddenly stopping atenolol can worsen angina, and sudden heart attacks. The dosage of antenol can be reduced steadily in some weeks.

If someone have chest pain or have heart disease do not stop using this drug suddenly. The condition may become bad. If doctor decides that no longer use this drug, you must gradually decrease the dose according to his directions. While decrease the dose, limit the physical activity to decrease the effort on the heart.

b)

Neostigmine is made up of reacting 3-dimethylaminophenol with N-dimethylcarbamoyl chloride, which produces a dimethylcarbamate. Then the product is alkylated using dimethylsulfate, which forms neostigmine. It facilitates myoneural connection impulse dispersion by inhibiting acetylcholine demolition by cholinesterase. Neostigmine is consumed by the liver by microsomal enzymes and undergoes hydrolysis by cholinesterase. Suggestive manage of myasthenia gravis; antidote for non depolarizing neuromuscular blocking agents after surgery; preclusion and action of postoperative distention and urinary retention

The representation of rapid eye movement sleep has contributed extensively to considerate nap neurobiology and sleep dependent respiratory gloominess. The representation has been used broadly in cat and rat, but old studies have established cholinergic REM sleep development in mouse. The nearby study used microinjection of neostigmine into pontine reticular formation of mouse to test the theory that attractive pontine cholinergic neurotransmission would cause amplified REM sleep and sleep messy breathing.

Behavioral clarification and physical scoring of polygraphic recordings showed that neostigmine formed a sleep like state. EEG power examination is done by the Fast Fourier Transformation established that pontine neostigmine caused EEG launch. Plethysmography established considerably disordered inhalation. The pontine microinjection of neostigmine decreased respiratory rate and minute exposure to air. Pontine neostigmine radically

increased period of stimulation and termination above waking levels and decreased inspiratory flow. More studies developed shown that pontine neostigmine considerably dejected locomotor action.

This learning is the primary to show cholinergic REM sleep development in anaesthetized, intact mouse. The outcome support upcoming studies to distinguish similarities and differences in cholinergic REM sleep enhancement in supplementary inbred strains and in transgenic mice. These comparisons will help distinguish sleep and breathing as transitional phenotypes that are found, by the lower level phenotype of pontine cholinergic neurotransmission.

c)

The effects of drug are using olfactory and trigeminal psychophysical measures; nasal patency was treated by means of anterior rhinoresistometry. Treating with ephedrine it produced a affinity towards an increase of nasal airflow. During the time of inspection there was no major dissimilarity between things produced by the dosages. Ephedrine had no regular effect on procedures of olfactory function. The only important correlation to the nasal airflow was found for supposed intensity of the trigeminal stimuli, which increased with increasing flow. Ephedrine appeared to have neither negative nor main optimistic belongings on intranasal chemosensory function in healthy subjects. This indicates that ephedrine may be used in studies on olfaction.

The study was to examine the things of ephedrine, an alpha, beta adrenoceptor agonist, on the directive of human nasal ciliary beat incidence.

<https://assignbuster.com/concepts-of-pharmacodynamics/>

At approximately 25 degrees C, we found that ephedrine induces an immediate and reasonable increase in human nasal CBF followed by an inhibitory response. While the increase is self-sufficient of ephedrine absorption, the inhibitory result is dependent on the concentration of ephedrine. These results we propose that the clinically used absorption of ephedrine has utmost stimulatory effect without clear inhibitory result on human nasal.

To expect the toxicity of nasal formulations, various in vitro and in vivo techniques have been used. Many of these techniques are very sensitive and it is a general problem to extrapolate the results to the clinical situation. The plan of the study was to set up a clinically well known nasal formulation, Ephedrine Nasal Drops, as a relevant reference for other nasal formulations with respect to histological changes to and reversibility of the nasal mucosa after repeated short-term nasal application to rabbits. This ephedrine formulation also contains the well known local irritants, benzalkonium chloride and EDTA, which is why it is abbreviated to EBE. Seventy five $\frac{1}{4}$ 1 was applied in one nasal cavity of rabbits four times per day for 1 week, while the other cavity served as a control. Twelve rabbits were divided into four groups and were sacrificed at after last nasal application, respectively. The macro- and microscopical changes of the nasal mucosa were recorded. Except for minor greyish exudates seen at 4 h, and a slight congestion of the mucosa seen at 4 and 24 h after application, there were no gross changes of the nasal mucosa. The microscopical examination, however, showed an extended infiltration of the mucosa by eosinophils, a general inflammatory reaction and a pronounced atrophy and disorganisation of the epithelium,

which was furthermore void of goblet cells and cilia. These microscopical changes were seen after 4 h and, to a minor extent, 24 h after application. After 7 days, no changes could be found, indicating that they were reversible in less than 1 week. It is concluded that EBE may be a good reference in the predictive testing of local toxicity, with respect to a cost/benefit evaluation of nasal formulations, meant for acute or short-term treatment.