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Doctor 2021 - رَوح - medicine - MU

pharmacology sheet

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PHARMACODYNAMICS

INDIVIDUALS USUALLY SHOW VARIATION IN INTENSITY OF RESPONSE TO DRUGS DUE TO:

1. Variation in concentration of drug that reaches the tissue receptors: due to pharmacokinetic factors

2. Abnormality in receptor number or function:

either genetically determined or acquired due to up- regulation or down-regulation

3. post-receptor defect inside cells:

This is an important cause of response variation

4. Variation in Concentration of an Endogenous Receptor Ligand

contributes greatly to variability in responses to pharmacologic antagonists.

B. QUANTAL DOSE–RESPONSE RELATIONSHIPS

By trials (for example determine the death but in animals)

Quantal mean a group, subject

the influence of the magnitude of the dose on the proportion of a population that responds.

I measure the effect of drug on the group so I look to the response of drug in a group

The measure of response of drug done by pharmacologist but in graded no

➢ **These responses are known as quantal responses, because, for any individual, the effect either occurs or it does not.**

The desired response is either:

A. Specified in amount or magnitude:

e.g., increase in heart rate of 20 beats/min by a drug that stimulates heart.

If the recorded response in any individual shows this amount or more, then this is regarded as positive response; otherwise, the response is negative

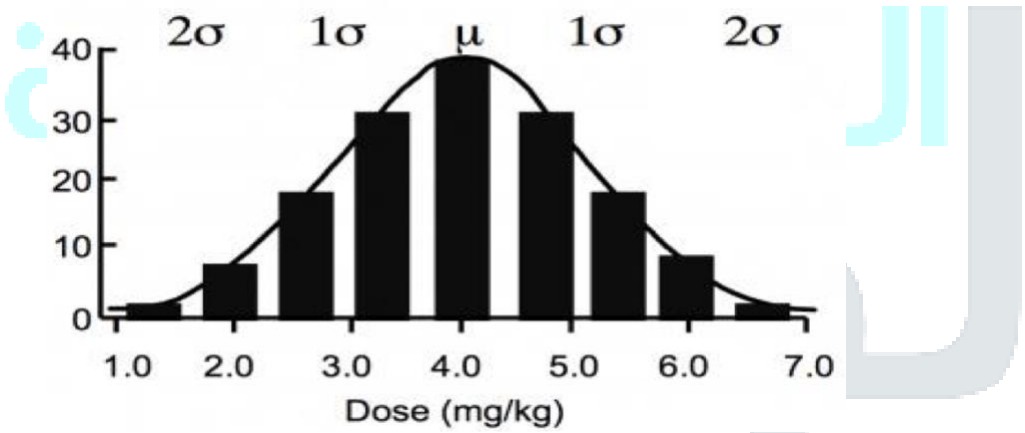
B. All-or-none response:

e.g., death; prevention of epileptic seizures; prevention of cardiac arrhythmias

the take of drug is frequency in trials

➢ For most drugs, the doses required to produce a specified quantal effect in individuals are lognormally distributed, i.e. a frequency distribution of such responses plotted against the log of the dose produces a gaussian normal curve of variation.

Determines minimum dose at which each patient responded with the desired outcome. The results have been plotted as a histogram and fit with a gaussian curve. μ = mean response; σ = standard deviation.



We have frequency dose of drug , use it to determine the mean: so the mean have SD (standard deviation)

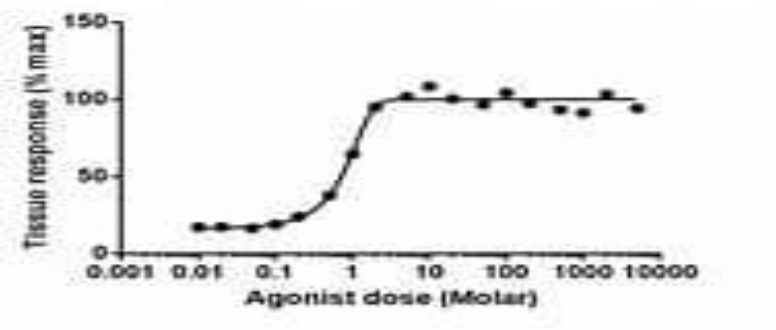
➢ When these responses are summated, the resulting cumulative frequency distribution constitutes a quantal dose-effect curve of the proportion or percentage of individuals who exhibit the effect plotted as a function of log dose

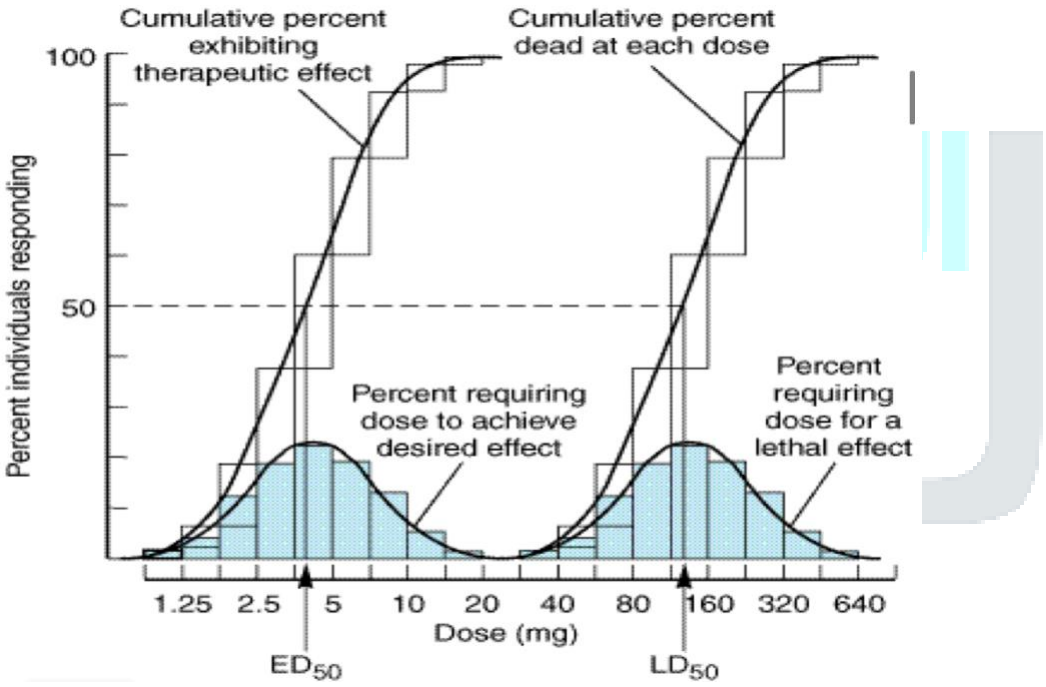
Example:

▪At 1.25mg/L, 2% respond, and 2.5mg/L 3% respond,

▪ Then at 1.25mg/L plot 2%, and at 2.5mg/L plot (2+3 = 5% etc.)

☠EXTRA☠ توضيح لفكرة المحنى السابق





quantal curve منحنى المجموعto all patient

➢ **The quantal dose-effect curve is often characterized by:**

1. median effective dose (ED50): the dose at which 50%

of individuals exhibit the specified quantal effect. differs from EC50

2. median toxic dose (TD50): the dose required to produce a particular toxic effect in 50% of Animals.

3. Median lethal dose (LD50): the dose required to produce a death in 50% of Animals.

The different between ED, EC

EC: talk about concentration in graded ,and give response

Ed: talk about effect of dose, and give what patient has response

SUMMATION AND POTENTIATION

Two common types of "agonistic" drug interactions are:

Agonistic : A drug that combines with the receptor to enhance the effect

1. Summation: When two drugs with similar mechanisms

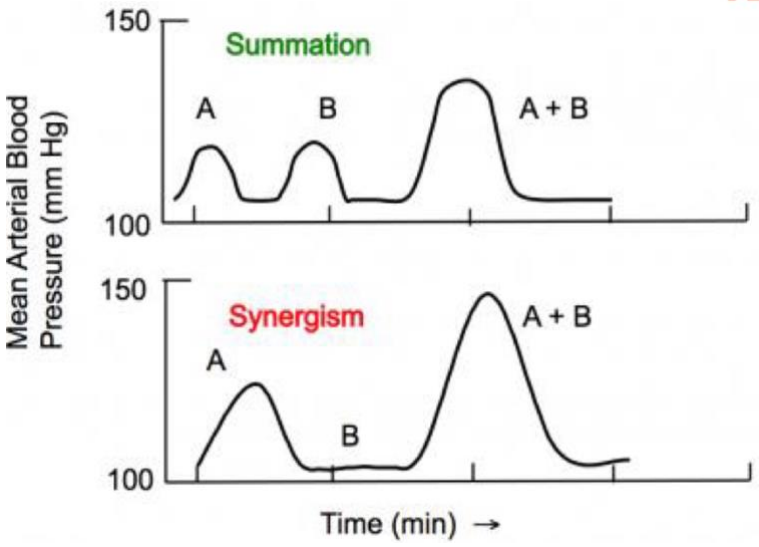
are given together, they typically produce additive effects. A drug +B drug =AB EFFECT of drug without exceeds effect

2. Potentiation or synergism: if the effect of two drugs

exceeds the sum of their individual effects. (Two drug have different mechanism) A drug +B drug =AB EFFECT of drug with exceeds effect

➢Potentiation requires that the drugs act at different receptors or effector systems.

Example of potentiation would be the increase in beneficial effects noted in the treatment of AIDS by combination therapy with AZT (a nucleoside analog



that inhibits HIV reverse transcriptase) and a protease inhibitor (protease activity is important for viral replication) .

PREDICTION OF DRUG SAFETY IN MAN

The most important thing when we give two drugs is a ((((safety))))))

➢ **This may be obtained from knowledge of Therapeutic Index (TI) of drug.**

the ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in a population of individuals

TI = TD50 / ED50

How can we get this value?

From quantal dose response (that get it from trials)

where :

TD50 = the drug dose that produces a toxic effect in half the population

ED50 = the drug dose that produces a therapeutic effect in half the population.

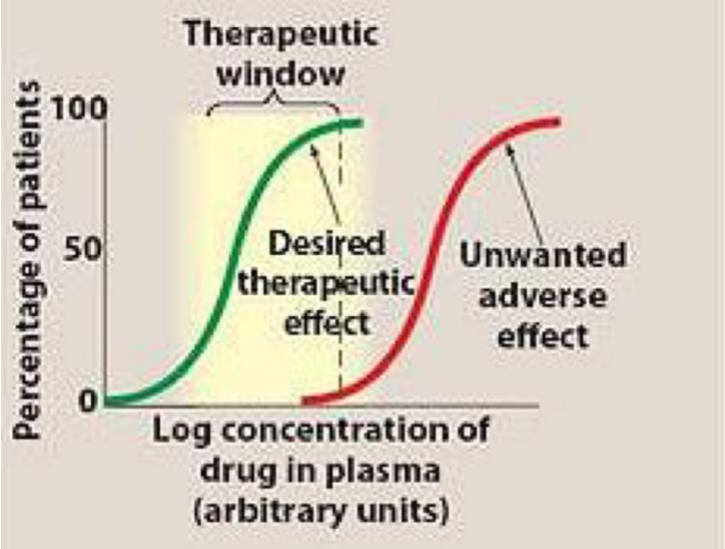
➢ **A larger value indicates a wide margin between doses that are effective and doses that are toxic.**

➢ **TI is determined by measuring the frequency of desired response, and toxic response, at various doses of drug.**

➢ **In humans, the therapeutic index of a drug is determined using drug trials (so it quantal) and accumulated clinical experience. These usually reveal a range of effective doses and a different (sometimes overlapping) range of toxic doses.**

➢ **The concentration range over which a drug produces its therapeutic effect is known as its therapeutic window**

- **when the therapeutic index is low, it is possible to have a range of concentrations where the effective and toxic responses overlap Agents with a low therapeutic index are those drugs for which bioavailability critically alters the therapeutic effects**



✓ **Narrow therapeutic index: in 100% effect start give side effects**

What is the problem: When we take overdose from it, because it very potent

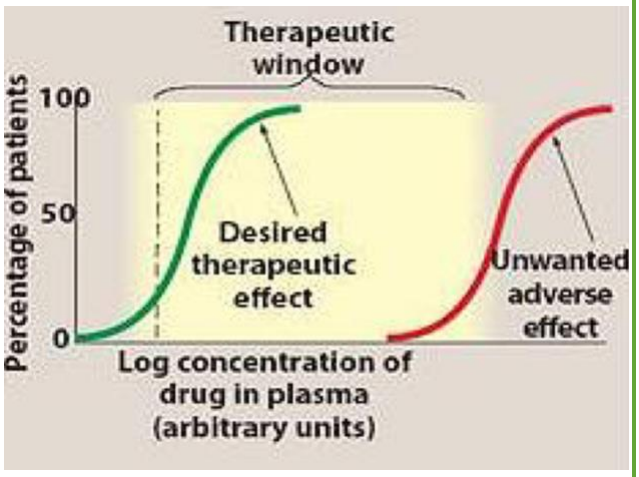
Endotoxins are very potent

The narrow therapeutic index controls any problem in absorption or in bioavailability (which is the amount of drug reach the blood}.

For example: Digoxin are very potent 50 micro gram but Panadol 500 milligram

✓ **Wide therapeutic index: bioavailability not play role in it**

Also overdose not affect, for example Panadol



➢**When therapeutic index is large, it is safe and common to give doses in excess (often about ten-fold excess) of that which is minimally required to**

achieve a desired response. In this case, bioavailability does not critically alter the therapeutic effects.

SPECIFICITY VS. SELECTIVITY

➢ **Specificity : If a drug has one effect, and only one effect on all biological systems it possesses the property of specificity.**

a drug that has a particular effect and not another.

➢ **Selectivity: refers to a drug's ability to preferentially produce a particular effect and is related to the structural specificity of drug binding to receptors.**

a drug that acts on a particular target (receptor) and not another

➢ **For example, a drug binds on a particular receptor-target (so its selective),**

The Selectivity more important than specificity

Example Beta Blockers not specific because it give effect on beta adrenorgeic receptors in the same time give different effect on beta adrenergic receptors in lung

But its Selectivity, in both (heart or lung) use beta receptor not alpha but not Specificity because cause differ effect

but that target may be expressed in different tissues and thus may exert different biological effects (so no specific).

ADVERSE EFFECTS OF DRUGS

These are unwanted and/or harmful effects

I. Predictable or dose-related or type A effects:

A. Side effects: These occur at therapeutic doses of a drug. They are usually minor, and{ decrease or disappear on reducing dose or sometimes with continued use of drug due to tolerance of the receptor that cause side effect }

B. Toxic effects: These are due to large toxic doses. They are usually serious, and need stopping drug use, and sometimes supportive treatment to save life is needed.

They may be:

1. **Functional e.g., respiratory depression (example morphine, pethidine)**
2. **Structural: causing tissue damage e.g. damage to liver or kidney or heart or nerves**

II. Unpredictable or Type B reactions :

(not affect by dose) NO DOSE - RELATED

A. Allergy:

This is due to activation of immune mechanisms by drug. Drug acts as hapten to induce formation of antibodies by plasma cells or to sensitize T-lymphocytes .example allergy to penicillin

Usually, allergic reactions have no dose-response relation; they are of 4 main types :

Type 1: Immediate type; it is the commonest type ; it is mediated by IgE antibodies that bind to membrane of mast cells in tissues or basophils in blood.

After re-exposure and binding to their specific antigen, they trigger release of histamine and other mediators from granules of these cells.

This causes urticaria or, in severe cases, anaphylactic shock which is a life threatening emergency

Type 2 : Cyto-toxic reaction :

mediated by either IgM antibodies in plasma or IgG antibodies that causes tissue damage by fixing complement and activating complement cascade

e.g. hemolysis; liver or kidney damage.

Type 3: Immune complex mediated reaction:

Circulating immune complexes formed between antigen and IgG antibodies which become deposited in capillaries of skin, joints, and kidney. Clinical features occur after many days of exposure to drug e.g., serum sickness

Type 4: Delayed cell-mediated reactions:

These are due to activation of sensitized T lymphocytes which release their cytokines and attract macrophages to site that also release tissue damaging cytokines

B. Idiosyncrasy:

abnormal drug reactions due usually to genetic factors affecting tissue enzymes or receptors.

Examples:

a. Hemolysis by sulfonamides or the antimalarial drug primaquine in patients with genetic deficiency of the enzyme glucose-6-phosphate dehydrogenase (G-6-PD) in their RBC (enzyme does not present because genetic problems)

b. Resistance to vitamin D or to the oral anti-coagulant warfarin

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III. Special toxicity including

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1. Genotoxicity leading to Mutagenicity: anticancer drug effect on the DNA cause gene toxicity

Alkylating agents

2. Teratogenicity:

Congenital disorder: drugs taken in pregnancy

3. Carcinogenicity: may take about 2 years. (anticancer drug causes secondary cancer after 2,3 years of used it)

- may be related to mutagenicity but less than is the case with teratogenicity

4. Reproductive toxicity recording pregnancy rate, number of live or stillbirths, & postnatal growth

IV. Others

1. Delayed toxicity: occurs sometime after stopping drug use e.g. idiosyncratic aplastic anemia due to chloramphenicol

2. Chronic toxicity: occurs with prolonged use of drug e.g. Cushing syndrome (moon face) from long-term use of steroids (example cortisone)

3. Dependence: occurs with prolonged use of CNS depressants e.g. alcohol; opioids like morphine

Adverse effects may be caused by :

1. Over-extension of same mechanism of action on same target tissue: e.g. Sedative-hypnotics; anticoagulants ; beta-adrenoceptor blockers

2. Effect on same receptor type but in another tissue: benefit in heart for example but adverse in lung

e.g., anti-muscarinic drugs; beta-blockers

3. Effect on different receptor or by different mechanism on target or other tissues example dopamine bind to alpha and beta receptor not selectivity <high adverse effect

The following groups are more susceptible to adverse drug reactions: fetus during pregnancy; elderly ; patients receiving many drugs (polypharmacy); patients with pre-existing disease ; patients with genetic enzyme defects in liver (poor oxidizers or slow acetylators) or tissues

" بطريقةٍ مَا ستُدرك أنَّك لستَ مالِك أمرك،وأنّ أمرَك وإنْ ضاقَ واستَضاقَ، لهُ ربٌّ هُو أولىٰ بهِ،وأنّ الله رحيمٌ، رحيمٌ بالقدرِ الذِي يُنجّينا منْ شُرورِ البشرِ،ومن أنفسِنا حينَ لا نقوىٰ عليهَا."