Drug dosage, Fixed dose combination & factors modifying drug action

Drug dosage

- Dose

  "Is the appropriate amount of a drug needed to produce a Certain degree of response in an individual"
- It varies with the chosen clinical response and type of therapy
- Prophylactic, therapeutic or toxic

- Standard dose
- Regulated dose
- Target level dose
- Titrated dose

Fixed dose ratio combination

ADVANTAGES

- Convenience and better compliance
- Synergistic
- Counters side effects
- Overcomes drug resistance
- Addition of therapeutic effect

Convenience and compliance - Rational
Convenience - Irrational

Disadvantages

- All the drugs are needed?
- Dose adjustment of one component is not possible
- Difference in the time course of action
- Adverse effect – difficult to spot the drug
- Contraindication to one component ---→ whole preparation
- Altered renal or hepatic function may affect PK,s of a drug

Factors modifying drug action

- Variation in response to the same dose of a drug between different patients and even in the same patient on different occasions is a rule rather then exception.

- Differ in pharmacokinetic handling of drugs.
- Variations in number or state of receptors, coupling proteins.
- Variations in neurogenic/ hormonal tone.

  Their understanding can guide choice of appropriate drug and dose for an individual patient.

Factors modify drug action either

- Quantitatively: plasma concentration/ action of the drug is increased or decreased-dealt with by adjustment of dosage
- Qualitatively: type of response is altered eg;allergy.

FACTORS MODIFYING DRUG ACTION

1. **BODY SIZE (drug conc at the site of action)**

$$\text{Dose} = \frac{\text{Weight in Kg}}{70} \times \text{Adult dose}$$

- $$\text{Dose} = \frac{\text{BSA } (m^2)}{1.7} \times \text{Adult dose}$$
- $$\text{BSA } (m^2) = \text{Wt } (kg)^{0.425} \times \text{Height } (cm)^{0.725} \times 0.007184$$

Activity

Calculate the dose of drug X to be administered for a child weighing 31.5 kgs and suffering from fever of unknown origin (adult dose of X= 500Mgs/dose)

Ans: 225mgs/dose

2. **Age**: for children

Young's Formula

$$\text{dose} = \frac{\text{Age}}{\text{Age} + 12} \times \text{Adult dose}$$

Dilling's Formula

$$\text{Dose} = \frac{\text{Age}}{20} \times \text{Adult dose}$$

Do infants have physiological differences...?

- GFR and tubular transport
- Hepatic drug metabolizing system
- Drug absorption
- Special adverse effects of drugs eg. Corticosteroids, androgens etc.

ELDERLY

- ↓ Renal function decreases and hence GFR
- ↓ hepatic drug metabolizing activity
- ↓ liver blood flow
- TOXICITY
- Low plasma albumin, reduced blood flow and motility of intestines, multiple drug therapy.

3.SEX

- Body size
- Gender specific- adverse effects of drugs

  antihypertensives – impotence & loss of libido

  ketoconazole - gynaecomastia
- Androgens are unacceptable to women and oestrogens to men
- In women considerations should be given to pregnancy and lactation.

Drugs in pregnancy

- ↓GI motility ↓ A
- ↑Plasma & ECF ↑ D
- Hepatic microsomal enzymes induction ↑ M
- ↑ Renal blood flow ↑ E
- Plasma proteins

  ↓ Albumin- ↑ unbound fraction of acidic drugs

  $\alpha 1$ acid glycoprotein – vice versa

4.Species & Race

- Rabbits are resistant to atropine.
- Rats are more sensitive to curare than cat

- Racial differences eg: blacks require higher and mongols require lower concentrations of atropine and ephedrine to dilate their pupil

- βblockers – less effective in blacks

5.Genetics

- Key **determinants of drug response** like transporters, ion channels, receptors, drug metabolising enzymes are **genetically controlled**.
- **Pharmacogenetics-** study of genetic basis for drug response variability
- **Pharmacogenomics** - use of genetic information to guide selection of drugs and dose in an **individual(tailor made or personalized therapy**)

- **Gene library!!**

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Genetic variations…

- **G6PD deficiency-** haemolysis by primaquine
- **Atypical pseudocholinesterase** – prolonged succinylcholine apnoea.
- **CYP2C9 variant-** increased action of warfarin
- **Isoniazid acetylation** by NAT2
- **Overexpression of P-gp** results in tumour resistance to anticancer drugs

6.Route of administration

- Governs speed & intensity of drug response
- Therapeutic response may depend on it
- Ex.Mgso4

7.Environmental factors and time of administration

- Hypnotics taken at night – work easily
- Insecticides, tobacco smoke and charcoal broiled meat are known to induce drug metabolism.
- Food interferes with absorption

Charcoal broiled meat

8. Psychological factors

- Patient's attitude and beliefs

  ex. Nervous and anxious patients require more Gen.Anaesthetics

- Placebo: inert substance - 'I shall please'
- Control device in clinical trial of drugs.
- To treat a patient who in the opinion of the physician does not require an active drug.
- Nocebo

Activity 1

Rate of elimination of a new drug is 20mg/hr at a steady state plasma concentration of 10mg/L, then its renal clearance will be……..

A)0.5 L/hr

B)2.0 L/hr

C)5.0 L/hr

D)20 L/hr

Ans: B

Clearence= elimination rate /pl.conc

9.Pathological states

- G.I.Diseases: alter absorption

  achlorhydria-decrease aspirin absorption

  NSAID's - aggrevate peptic ulcer
- Liver disease: bioavailability of drugs having high first pass metabolism is increased.
- Serum albumin is decreased. eg;warfarin
- Metabolism and elimination of some drugs is decreased and their dose should be reduced,eg; morphine.
- Prodrugs. Eg; bacampicillin

CHF

- decreasing drug absorption from g.i.t due to mucosal oedema and splanchnic vasoconstriction.
- Modify Vd.
- Retarding drug elimination as a result of decreased perfusion and congestion of liver, decreased GFR and increased tubular reabsorption.

KIDNEY DISEASE

- Clearance of drugs that are primarily excreted unchanged is reduced parallel to decrease in creatinine clearance. Eg; aminoglycosides.
- BBB permeability increased
- Thyroid disease: clearance of digoxin is roughly proportional to thyroid function.

- others: antipyretics in fever
  diuretics in edema

10.Drug interactions

- Drugs may modify the response to each other by pharmacokinetic or pharmacodynamic interaction between them.
- Eg; allopurinol and ampicillin - high incidence of skin rashes

11.Cumulation

- Any drug will cumulate in the body if rate of administration is more than rate of elimination.
- Eg; prolonged use of chloroquine causes retinal damage.

12.Tolerance

- Requirement of higher dose of a drug to produce a given response.
- Natural: eg;-species-rabbits are tolerant to atropine
  - Race-blacks are tolerant to mydriatics

ACQUIRED

- By repeated use of a drug in an individual who was initially responsive. eg;-CNS depressants.
- Tolerance need not develop equally to all actions of a drug.eg;- tolerance occurs to analgesic and euphoric actions of morphine but not to its constipating and miotic actions.

Cross tolerance

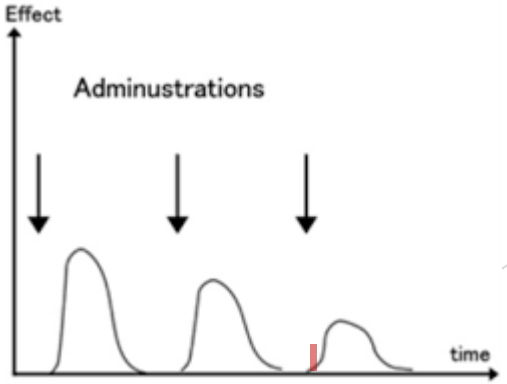
- Development of tolerance to pharmacologically related drugs.eg;- alcoholics are relatively tolerant to GAs.
- Mechanisms may be
- Pharmacokinetic-effective concentration at the active site is decreased- by enhancement of drug elimination on chronic use eg;- barbiturates

- **Pharmacodynamic/cellular tolerance: cells of the target organ become less responsive –may be due to down regulation of receptors.**

Tachyphylaxis

- Rapid development of tolerance-doses of a drug repeated in quick succesion result in marked reduction in drug response- usually seen with indirectly acting drugs.
- Eg; ephedrine-act by releasing catecholamine's in the body, synthesis of which is unable to match release-stores get depleted.

TEA or TEN



Drug resistance

- Refers to tolerance of microorganisms to inhibitory action of antimicrobials.
- Eg; staphylococci to penicillin.

Question. 1

percentage of a drug remaining in the body after 5 half lives which follows 1st order kinetics is…….

A) 6.25%

B) 96.875%

C) 93.750%

D) 94.750%

E) None of the above

E) None of the above

Question 2

True about first order kinetics is

A) clearence remains constant

B) fixed amount of drug is eliminated

C) half life increases with dose

D) decreased clearence with increasing dose

Ans: A