CHAPTER-II

Design of dosage regimens

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Paracetamol 500 mg/tab
Sig. Take 1 tab every 4 hours for fever

Mefenamic acid 500 mg/tab
Sig. Take 1 tab every 6 hours for pain
Penicillin G 1,000,000 u/IV q8

Penicillin G 1,000,000 u/IV q6

Gentamycin 80 mg/IV OD
Approaches:

- Empirical
- Kinetic
Empirical approach

- Involves administration of a drug in a certain quantity, noting the therapeutic response
- After which the dosage and the dosing interval modified
Empirical approach

- Employed when the drug concentration in serum or plasma does not reflect the concentration of drug at the receptor site in the body
Empirical approach

- Pharmacodynamic effect of the drug is not related (or correlated) with the receptor site
- Serum levels is not proportional to the clinical outcome
Empirical approach

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Empirical approach

- Anticancer drugs
- Warfarin = INR (International Normalized Ratio)
- Dopamine drip = central venous pressure
- Insulin sliding scale = RBS
Pharmacokinetic approach

- Assumption: therapeutic & toxic effects are proportional to the plasma conc. of drug at the receptor sites or amount of drug in the body.
Pharmacokinetic approach

- Knowledge on the ADME of the drug from a single dose can determine or estimate the plasma levels of it when given at multiple doses
Factors that determine a dosage regimen

- **Activity-Toxicity of the drug**
  1. Minimum therapeutic dose/MEC
  2. Toxic dose/MTC
  3. Therapeutic index
  4. Side effects
  5. Dose-response relationship
Factors that determine a dosage regimen

- **Pharmacokinetics**
  1. Absorption (rate of diffusion, dissolution, disintegration, gastric emptying time)
  2. Distribution (protein-binding)
  3. Metabolism (biologic half-life)
  4. Excretion (drug clearance)
Factors that determine a dosage regimen

- Clinical Factors
  1. Clinical state of the patient
     a. Age, weight, urine pH
     b. Condition being treated (life-threatening or not)
     c. Existence of other disease states (Co-morbidities)
Factors that determine a dosage regimen

- Clinical Factors
  2. Management of therapy
    a. Multiple drug therapy
    b. Convenience of regimen
    c. Compliance of the patient
Factors that determine a dosage regimen

- Tolerance-dependence
- Pharmacogenetics-idiosyncrasy
- Drug interactions
- Dosage form and route of administration
Administration may be given once for its desired therapeutic effect (e.g. antihelmintic medications) or for a period of time through multiple doses.
Goal for Multiple Doses

- Maintain the plasma or serum concentration (Cp) within the therapeutic index
- Greater than or less than? 
  _______ MEC and _______ MTC
A drug will accumulate in the body when the dosing interval is less than the time needed for the body to eliminate a single dose (parameter? ________________)
Scenario

- 50 mg drug with a half life of 12 hours with a dosing interval of 8 hours
Steady State
- Attained after approximately four half-times
- Time to steady state independent of dosage

Steady State Concentrations

CONCENTRATION

TIME (multiples of elimination half-time)
Important variables

- Dose size \((D)\)
- Dosing interval \((\tau)\)
- Mean steady state blood conc.
- Maximum state blood conc.
- Minimum steady state conc.
Principle of superposition

- Assumes that early doses of the drug do not affect the pharmacokinetics of subsequent doses.
- Plasma levels after the 2\textsuperscript{nd}, 3\textsuperscript{rd} or nth dose will overlay or superimpose the blood level attained after the (n-1)th dose.
Principle of superposition

- Allows one to project the plasma conc.-time curve of a drug after several consecutive doses based on the plasma conc.-time curve obtained from a single dose
Assumption:

- Drug is eliminated by first-order kinetics
- Pharmacokinetics of the drug after a single dose (first dose) is not altered after taking multiple doses
Superposition cannot be applied

- Pathophysiology of the patient
- Saturation of the drug carrier system
- Enzyme induction or inhibition
Steady state or plateau concentration

- The amount of drug lost per interval is replenished when the drug is given again.
- Consequently, the Cp of the drug fluctuates between a minimum conc. & a maximum conc.
Steady state or plateau concentration

- AUC of the dosing interval during the steady state = AUC for a single dose
Steady state or plateau concentration

- It is optimal to TARGET dosing so that the plateau conc. resides within the therapeutic index
Considerations in designing a dosage regimen

- Assumed that all pharmacokinetic parameters are constant. In case one of these factors are changed, dosage regimen is no longer valid.
Considerations in designing a dosage regimen

- Change in urinary pH can cause deviation of blood levels from calculated ones.
- Change in renal function will prolong elimination of drugs (esp. excreted in unchanged form via the kidneys) = blood creatinine/creatinine clearance.
Considerations in designing a dosage regimen

- Change in hepatic clearance due to liver disease or saturation of metabolic pathways, enzyme induction or enzyme inhibition can alter the elimination of drugs
Considerations in designing a dosage regimen

- Congestive heart failure and myocardial infarction may cause reduction in blood flow $\rightarrow$ reduced $Vd$ and prolong elimination of drugs
- Equations are based on the open-one compartment model
Therapeutic Drug Monitoring
Therapeutic Drug Monitoring

- Individualization of dosage to optimize patient responses to drug therapy
- Aims to promote optimum drug treatment by maintaining serum drug conc. (SDC) within a therapeutic range
Therapeutic Drug Monitoring

- Practice applied to a small group of drugs where there is a direct relation between SDCs and pharmacologic response but a narrow range of conc. that are effective & safe (narrow therapeutic window)
Therapeutic Drug Monitoring

- Term used interchangeably with clinical pharmacokinetics
Assumptions:

- Measuring patient SDC provides an opportunity to adjust for variations in patient pharmacokinetics by individualizing drug dosage.
- SDC is a better predictor of patient response than is dose.
Assumptions:

- Good relation between SDCs and pharmacologic response
- Drug metabolism varies between individuals
Indications of TDM

- Drugs with narrow therapeutic index (e.g. Lithium)
- Patients with impaired clearance of a drug with a narrow TI (e.g. renal failure receiving gentamycin)
Indications of TDM

- Drugs whose toxicity is difficult to distinguish from a patient’s underlying disease (e.g. Theophylline in patients with COPD)
- Drugs whose efficacy is difficult to establish clinically (e.g. Phenytoin)