- Dose required to produce a certain response varies from individual to individual, this is called inter subject variability.
- Rational drug therapy requires individualization of dosage regimen to fit a patient's need.

- Dosing in elderly patient:

- The geriatric population is often arbitrarily defined as patients who are older than 65 years, and many of these people live active and healthy lives
- In addition, there is an increasing number of people who are living more than 85 years, who are often considered as the older elderly population.
- The aging process is more often associated with physiological changes during aging rather than purely chronological age.

- Chronologically, the elderly have been classified as:

1. Young old (ages 65-75 years)
2. The old (ages 75-85 years)
3. The old-old (age above 85 years)

- Performance capacity and the loss of homeostatic reserve decreases with advanced age but occurs to a different degree in each organ and in each patient.
- Physiologic and cognitive functions tend to change with the aging process and can affect compliance and the therapeutic safety and efficacy of a prescribed drug.
- The elderly also tend to be on multiple drug therapy due to concomitant illness.
- Decreased cognitive function

• Complicated drug dosage schedules
• High cost of drug therapy
- Several vital physiologic functions related to age as measured by markers show that renal plasma flow, glomerular filtration, cardiac output and breathing capacity can drop from 10% to 30% in elderly subjects compared to those at age 30.
• The physiologic changes due to aging may necessiate special considerations in administering drugs in the elderly which is due to an age dependent increase in adverse drug reactions or toxicity may be observed.
• This apparent increased drug sensitivity in the elderly may be due to pharmacodynamic and pharmacokinetic changes.
• The pharmacodynamic hypothesis assumes

that age causes alterations in the quantity and quality of target drug receptors leading to enhanced drug response.

Quantitatively, the number of drug receptors may decline with age, whereas qualitatively, a change in the affinity for the drug may occur.

. The pharmacokinetic hypothesis assumes that age dependent increase in adverse drug reactions are due to physiologic changes in drug ADME.

-Age dependent alterations in drug absorption may include:

- Decline in the splanchnic blood flow
- Altered gastrointestinal motility
- Increase in gastric pH
- Alteration in the gastrointestinal absorptive surface.

→ Age dependent alterations in drug distribution may include:

- Decreased drug protein binding in the plasma as a result of decrease in the albumin concentration.
- Change in the apparent volume of distribution due to decrease in muscle mass and increase in body fat.
- Renal drug excretion also generally declines with age as a result of decrease in GFR and active tubular secretion.
- The activity of enzymes responsible for drug biotransformation may decrease with age, leading to a decline in hepatic drug clearance.

$$\text{Patient's Dose} = \frac{(\text{weight, kg})\ 0.7 \times (140 - \text{age, year})}{1660} \times \text{adult dose}$$

◦ Dosing in Obese Patient:

Obesity is a major problem in the united states and is also becoming a problem in other countries.

• Obesity has been associated with increased mortality resulting from increases in the incidence of HTN, Atherosclerosis, Coronary Artery Disease, Diabetes and other conditions compared to non obese patients.

• A patient is considered obese if actual body weight exceeds ideal or desirable body weight by 20% according to Metropolitan Life Insurance company data.

• Ideal or desirable body weights are based on average body weights and heights for males and for females considering age.

• Athletes who have a greater body weight due to greater muscle mass are not considered obese.

• Obesity often defined by Body Mass Index (BMI) a value that normalizes body weight based on height.

• BMI is expressed as body weight (kg) divided by the square of the person's height (meters) or kg/m^2.

$$BMI = \left(\frac{\text{Weight in Pounds}}{(\text{Height in inches}) \times (\text{Height in inches})}\right) \times 703$$

$$BMI = \frac{\text{weight in kg}}{(\text{Height in meters}) \times (\text{Height in meters})}$$

• The obese patient (BMI > 30) has a greater accumulation of fat tissue than is necessary for normal body functions.

• Adipose (fat) tissue has a smaller proportion of water compared to muscle tissue. Thus, the obese

patient has a smaller proportion of total body water to total body weight compared to the patient of ideal body weight, which can affect the apparent volume of distribution of the drug.

- In addition to differences in total body water per kilogram body weight in the obese patient, the greatest proportion of body fat in these patients could lead to distributional changes in the drug's pharmacokinetics due to partitioning of the drug b/w lipid and aqueous environments

- Drugs such as digoxin and gentamicin are very polar and tend to distribute into water rather than into fat tissue, although lipophilic drugs are associated with larger volumes of distribution in obese patients compared to hydrophilic drugs.

• Other pharmacokinetic parameters may be altered in the obese patient as a result of physiologic alterations such as fatty infiltration of the liver affecting biotransformation and cardiovascular changes that may affect renal blood flow and renal excretion.

• Dosing by actual body weight may result in overdosing of drugs such as aminoglycosides (eg, gentamicin), which are very polar and are distributed in extracellular fluids. Dosing of these drugs are based on ideal body weight.

• Lean Body Weight has been estimated by several emperical equations based on the patient's height and actual (total) body weight.

• The following equations have been used for estimating lean body weight, particularly for adjustment of dosage in renally impaired patients:

LBW (males) = 50kg + 2.3kg for each inch over 5 ft

LBW (female) = 45.5kg + 2.3kg for each inch over 5 ft

Example:

Calculate the lean body weight for an adult male patient who is 5ft 9in (175.3cm) tall and weights 264lb (120kg).

-Solution:

LBW = 50 + (2.3 × 9) = 70.7 kg

▫Dosing in Pediatric patient:

- Dosing of drugs in this population requires a through consideration of the differences in the pharmacokinetics and pharmacology of a specific drug.
- Unfortunately, the pharmacokinetics and pharmacodynamics of most drugs are not well known in children under 12 years of age.
- The variation in body composition and the maturity of liver and kidney function are potential sources of differences in pharmacokinetics with respect to age.
- Infants are defined as children 0-2 years of age. However, within this group, special consideration is necessary for infants less than 4 weeks (1 month) old, because their ability to handle drugs often differs from that of more mature infants.

• In addition to different dosing requirements of the pediatric population, there is a need to consider the use of pediatric dosage forms that permit more accurate dosing and patient compliance.

• For example, liquid pediatric drug products may come with calibrated dropper or a premeasured teaspoon (5ml) for accurate dosing and have a cherry flavor for pediatric patient compliance

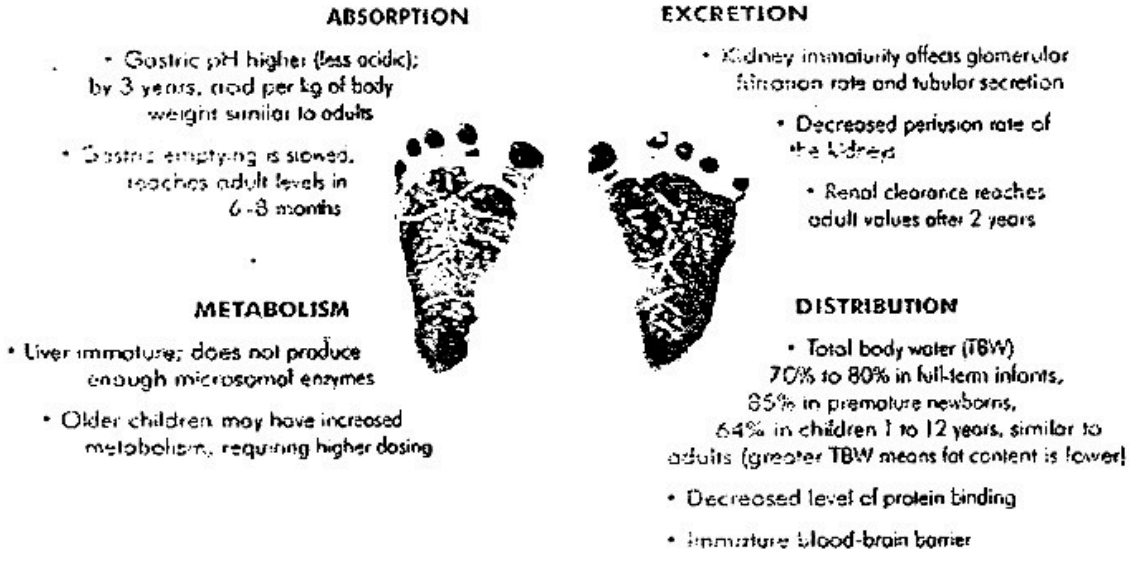
• Pediatric drug formulations may also contain different drug concentrations compared to the adult drug formulation.

• In general, complete Hepatic function is not attained until the 3rd week of life and oxidative process are fairly well developed in infants, but there is a deficiency of conjugative enzymes.

• In addition, many drugs exhibit reduced binding to plasma albumin in infants.

• Newborns show only 30%-50% of the renal activity of adults on the basis activity per unit of body weight and drugs that are heavily dependent on renal excretion will have a sharply decreased elimination half-life.

• For ex, the penicillins are excreted for the most part through the kidney and elimination half-life of such drugs are much reduced in infants.



□ Different methods to calculate the dose of drugs for infants and children are:

- Based on the Age
- Based on the Body weight
- Based on the Body Surface area

. Depending upon whether the dose was calculated for an infants or a child, the method use the age in year for the child and age in month for the infant, these methods are:

1. Fried's rule: (for infants and children up to 2 years)

$$\text{Dose} = \left(\frac{\text{Age in month}}{150}\right)(\text{adult dose})$$

2. Young's rule: (for children up to 1-12 years)

$$\text{Dose} = \left(\frac{\text{age in year}}{\text{age} + 12}\right)(\text{adult dose})$$

3. Cowling's rule:

$$\text{Dose} = \left(\frac{\text{Age in birthday}}{24}\right)(\text{adult dose})$$

4. Clark's rule:

$$\text{Dose} = \left(\frac{\text{Weight in lb}}{150}\right)(\text{adult dose})$$

- Another adjustment method is based on the body weight of the infants and children by the use of methods suchas:

5. Augus Berger method:

$$CD = \frac{(AD)\cdot(1.5) \times (CW + 10)}{100}$$

6. Crawford-terry-rourke method:

- Based on Body surface area of the infants and children:

$$BSA = \frac{(AD)\cdot(\text{body surface area of child})}{1.73\ m^2}$$

- Methods such as Young's rule or Clark's rule for dose adjustment are at best crude approximations in that they take into account only body age and size change attributable to growth and do not consider the rate of drug elimination.
- Other method which is based on the body surface area has the advantage of avoiding bias due to obesity or unusual body weight, because the height and weight of the patient are both considered.
- The body surface area method gives only a rough estimation of the proper dose, because the pharmacokinetic differences of specific drugs are not considered.

- Practice problem:
  - The elimination half-life of penicillin G

is 0.5 hour in adults and 3.2 hours in neonates (0-7 days old). Assuming the normal adult dose of penicillin G is 4 mg/kg every 4 hours, calculate the dose of penicillin G for an 11 pound infant.

-Solution:

$$\frac{T_1}{T_2} = \frac{(t_{1/2})_1}{(t_{1/2})_2}$$

$t_{1/2} = 0.5\,hr$

$T_2 = \frac{4 \times 3.2}{0.5} = 25.6\,hr$

-Therefore, this infant may be given the following dose:

$$\text{Dose} = 4\,mg/kg = 11\,lb = 20\,mg \text{ every } 24\,hr$$
$$2.2\,lb/kg$$

Alternatively, 10 mg every 12 hours would achieve the same (C_{av}).

1. Explain the principle of drug dosing in elderly [5m, Ay 11]

2. Briefly explain drug dosing in obese patients [2m, 14, 11]

3. Write the different methods for calculating child dose [2m, 14]

4. Explain the principle and method of determining drug dose in obese patients [5m, 10]

5. Write any two formulae (or two methods) used to calculate child dose of drugs. [2m, 10] [2m, Sep 11] [2m, Feb 12]

6. Dosage adjustment in Pediatrics is essential. Explain mentioning the different methods used in child dose calculation [5m, Sep 12]

7. Dosing of drugs in obese patients is important. Why? [2m, Sep 12]