DOSAGE REGIMEN ADJUSTMENT

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- Adjustment of DR in Infants, Neonates & Children
- Adjustment of DR in Obese Patients
- Adjustment of DR in Elderly People
- Adjustment of DR in Hepatic Disorder Cases
- Adjustment of DR in Renal Disorder Cases

ADJUSTMENT OF DR IN INFANTS, NEONATES AND CHILDREN

- Dosing of drugs in infants requires a thorough consideration of differences between the infants and that of adults, which concerns the pharmacokinetics and pharmacology of the drug.

- The variations in body composition and maturity of liver and kidney functions are the potential source of differences in pharmacokinetics w.r.t age.

- Infants are defined as the children between 0 – 2 Years of age.

- Within this group special considerations are necessary for infants less than 4 weeks old because of their ability to handle drugs often differs from more matured infants.

- In general hepatic function is not attained until 3rd week of life.
- Oxidative processes 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.
- New born show only 30 -40 % renal activity of adults on an activity per unit of body weight basis.
- Drugs that are heavily dependent on renal excretion will have sharply increased elimination half life.

- The dosage of drugs given to infants should be based on PK considerations.

- Two classic formulae for adjustment of doses in infants are…
- Clarks Rule:

  Child Dose = (Weight (lb) x Adult Dose) / 150
- Young’s Rule:

  Child Dose = Age(year)/Age(year)+12 x Adult Dose

- The growth above rules for dose adjustments are at best approximates that assume only body age and size changes with growth and do not consider the rate of elimination.

- Another dosage adjustment method is based on body surface area this approach has advantage to avoid bias due to obesity or unusual body weight since height & weight of the patient are both considered.

- Neonates, infants, children require different doses than adults because of difference in BSA , TBW & ECF on per Kg body weight basis.

- The dose for such patients are calculated on the basis of the BSA & not on body weight basis because BSA correlates better with dosage requirement , cardiac output , renal blood flow & glomerular filtration in children.

Mosteller's equation

$$\text{Surface area } (m^2) = (\text{height x weight})^{1/2}/60$$

- Infants & children require large mg/kg doses than adults
  - Their BSA /kg body weight is larger .
  - Larger volume of distribution (specifically TBW & ECF).
- Childs maintenance dose can be calculated from adult dose by the following equitation.

$$\text{Child dose} = \text{SA } (m^2)/1.73\text{xadult dose.}$$

$$SA\ (m^{2)})= (\text{Body weight Body in kg})^{0.7}$$

- Equation for calculating child dose

$$\text{child dose} = [\text{weight of child(kg)}]^{0.7}/70 \times \text{Adult dose}$$

- TBW in infants is 35to 40% more than in adults. Hence
  - V_d for water soluble drugs is larger in infants
  - V_d for most lipid soluble drugs is smaller in infants

DOSAGE REGIMEN ADJUSTMENT IN OBESE PATIENTS

- Obese patients has greater accumulation of fat tissues than neccesary for normal body.
- Apparent volume of distribution is greatly effected by changes in body weight since body weight is directly related to volume of various body fluids.
- DR adjustment in obese cases will be considered w.r.t body wt

IBW (men) = 50kg ± kg /2.5cm above or below 150cm in height

IBW (women) =45 ± 1kg /2.5cm above or below 150cm in height

- Any person whose body weight is more than 25% above the IBW is considered as obese.

- For such obese patients ,the lean to adipose tissues composition or ratio is small because of greater proportion of body fat which alters the volume of distribution of the drug.

- In contrast athletes who have greater body weight due to greater muscle mass are not considered as obese.

- Adipose or fat tissue has smaller proportion of water compared to muscle. Thus patients small proportion of TBW to that of TBW (W- weight)compared to the patient with ideal BW which could effect V_d of drug.

- The ECF of adipose tissue is small in comparision to lean tissue in case of obesity patients.
  - For ex: 1. Digoxin do not significantly distribute in excess in body space so, V_d do not change& hence dose to be administered should be calculated on IBW bases but not w.r.t the change in the body wt
  - Ex;2.. Hydrophilic drugs like Gentamycin which distributes in excess body space of obese patients to extent less than that in lean tissue then the dose should be lesser on per kg TBWt. basis.
  - Ex;3 Drugs like theophylline , caffeine, lidocaine which distribute to same extent in both lean &adipose tissue then V_d is larger in obese patients but same on per kg TBW basis then the dose should be administered on TBW basis.

- Drugs like diazepam, phenytoin which are lipophilic & distribute more in adipose tissue. V_d is larger per kg BW in obese patients & hence require larger doses more than that on TBW basis.

- Changes in dose based on V_d alteration leads to modification of clearance & half life of drug.

- In addition to differences in TBW per kg Body Wt basis in obese patients the greatest proportion of body fat in obese patients could also leads to distribution changes in drugs PK due to partition of drug between lipid & aqueous environments.

- Other PK parameters that may altered in obese patients due to possible physiological alterations such as fatty infiltration of liver effecting biotransformation & cardiovascular changes which might also effect renal blood flow & renal excretion.

DOSAGE ADJUSTMENT IN ELDERLY PATIENTS

- The physiological changes due to aging may necessitate administering drugs to elderly people.
- The body composition of elderly patients is modified in many ways.
- The lean body may decrease & body fat increases by almost 100% in elderly patients as compared to adults.
- Since fatty tissues are increased & metabolic processes will be slow down.
  - For ex: fat soluble drugs may have an altered v_d due to increased amount of fatty tissues.

- Small vol. of body fluids and water higher peak alcohol levels are observed in elders subjects than in adults.

- Free drug conc. in the body increases because of reduced drug plasma-protein binding

- Cardiac output of the elderly patients is only slightly modified however perfusion of blood to intestinal regional is reported to be greatly reduced ,potentially effecting absorption of drug from the GIT.

- GFR is reduced significantly in elders creating longer elimination half- life with drug for renally excreted drugs & possibility for accumulation of drug, the receptor sensitivity in elders may be modified which may results in increased incidence of side effects in elderly patients.

- Hence dose should be reduced in elderly patients because of general decline of body function with age.

- Generalized eq. for calculation of maintenance dose for patient of any age except neonates & infants is given by :

Patients dose = (wt. in Kg $)^{0.7}$ (140~ age in yrs) / 1660 x Adult dose.

DOSAGE REGIMEN ADJUSTMENT IN HEPATIC DISORDERS

- Normally since liver is major site for drug metabolism utmost care should be taken in administering drugs to patients with liver diseases.

- The influence of hepatic disorder on drugs availability & disposition is unpredictable because of the multiple effects that liver disease produces resulting effects on drug metabolizing enzymes, on drug binding and hepatic blood flow.

- Disorders of liver results in alteration of various levels of hepatic enzymes in general hepatic clearance being increased in cirrhosis, infective hepatitis.

- Correlation between altered drug PK & hepatic function is often difficult.
  - For ex: unlike excretion there are numerous path ways by which a drug may be metabolized and each of them is effected to different extent in hepatic diseases.

- Depending on the disease the behaviour of the given drug changes as a result no change is detected for the same drug in some cases where as it alters signifying in some other disorders.

- Liver diseases not only changes the metabolism of the drug leading to increased half life & C_p values but it may also results in increased bioavailability of the drug.

- The reason for this liver disorder patients develop a portal bypass mechanism, a condition in which significant fraction of the portal blood supply by pass parenchymal tissue & directly enters the systemic circulation.

- Liver function disorder may not always suggest a decrease in dose, since some of the drugs not only depend on liver function or clearance, or half life or residence time but also on the V_d.

- In liver disorder the protein synthesis may be decreased, if it is a protein bound drug, the may remain unbound, it is the free form which is mainly excreted by kidney to a larger extent, as the kidney function is normal major portion of drug excreted in excess by kidneys, in which case the dose may be increased.

- Hepatic function may be regarded as a graded phenomenon which means the extent of liver damage should reflect any changes in PK parameters of the drug.