▫ Design of dosage regimens

Dosage regimen:

It is defined as the manner in which a drug is taken.

For some drugs like analgesics, hypnotics, antiemetics etc, a single dose may provide effective treatment.

However, the duration of most illness is longer than the therapeutic effect produced by single dose. In such cases, drugs are required to be taken on a repetitive basis over a period of time depending upon the nature of illness. Thus, for successful therapy, design of an optimal multiple dosage regimen is necessary.

• An optimat multiple dosage regimen is the one in which the drug is administered in suitable doses, with sufficient frequency that ensures

maintenance of plasma concentration within the therapeutic window for the entire duration of therapy.

Approches to design of dosage regimen:

1. Empirical dosage regimen
2. Individualized dosage regimen
3. Dosage regimen on populations averages
4. Dosage regimen based on partial pharmaco-kinetic parameters

1. Empirical Dosage Regimen: is designed by physician based on empirical clinical data, personal experience and clinical observations.

This approach is, however, not very accurate.

2. Individualaized dosage regimen: is the most accurate approach and is based on the pharm-

acokinetics of drug in the individual patient. The approach is suitable for hospitalised patients but is quite expensive.

3. Dosage regimen on population averages: It is the most often used approach.

The method is based on one of the two models:

- Fixed model
- Adaptive model

Fixed model: Here, population average pharmacokinetic parameters are used directly to calculate the dosage regimen.

Adaptive model: It is based on both population average pharmacokinetic parameters of the drug as well as patient variables such as weight, age,

sex, body surface area and known patient pathophysiology such as renal disease.

Nomograms And Tabulations in designing dosage regimens:

- A nomogram is a graphical calculating device a two dimensional diagram designed to allow the approximate graphical computation of a function
- A nomogram typically has 3 scales:
  - 2 scales represent known values and 1 scale is the where the result read off.
  - These scales may be linear, logarithmic or have some more complex relationship.
- For ease of calculation of dosage regimens, many clinicians rely on nomograms to calculate the proper dosage regimen for their patients.
- The use of a nomogram may give a quick

dosage regimen adjustment for patients with characteristics requiring adjustments, such as age, body weight, and physiologic state.

- In general, the nomogram of a drug is based on population pharmacokinetic data collected and analyzed using a specific pharmacokinetic model.
- In order to keep the dosage regimen calculation simple, complicated equations are often solved and the result displayed diagrammatically on special scaled axes to produce a simple dose recommendation based on patient information.
- Some nomograms make use of certain physiologic parameters, such as serum creatinine concentrations, to help modify the dosage regimen according to renal function.
- For many marketed drugs, the manufacturer provides tabulated general guidelines for use

in establishing a dosage regimen for patients, including loading and maintenance doses.

• For example, the initial dose's and subsequent serum monitoring of theophylline anhydrous sustained-action capsules and theophylline extended-release tablets are showing below respectively:

Table : Maintenance dose of theophylline when the serum concentration is not measured*

AGE	DOSE	DOSE PER 12 HOURS
6–9 yrs	24 mg/kg/day	12.0 mg/kg
9–12 yrs	20 mg/kg/day	10.0 mg/kg
12–16 yrs	18 mg/kg/day	9.0 mg/kg
Over 16 yrs	13 mg/kg/day or 900 mg, *whichever is less*	6.5 mg/kg

Table : Dosage Guidelines for Rapid Theophyllinization*

PATIENT GROUP	MAINTENANCE DOSE
Children 1–9 yrs	4 mg/kg every 6 hr
Children 9–16 and young adult smokers	3 mg/kg every 6 hr
Otherwise healthy nonsmoking adults	3 mg/kg every 8 hr
Older patients and patients with cor pulmonale	2 mg/kg every 8 hr
Patients with congestive heart failure	1–2 mg/kg every 8 hr

-for drugs with a narrow therapeutic range, such as theophylline, a guide for

monitoring serum drug concentration is given.

- Another example is the aminoglycoside antibiotic, tobramycin sulfate USP, which is eliminated primarily by renal clearance. Thus the dosage of tobramycin sulfate should be reduced in direct proportion to a reduction in creatinine clearance.

- The manufacturer provides a nomogram for estimating the percent of the normal dose of tobramycin sulfate assuming the serum creatinine level (mg/100 ml) has been obtained.

Methods:

1. The Siersback-Nielsen Nomogram:

- The nomogram method of Siersback-Nielsen estimates creatinine clearance on the basis of age, weight and serum creatinine concentra-

tion and gender of patient.

- The Nomograms consists of five vertical lines, drawn parallel to, and suitable distance from each other.

- These lines are labeled follow:

1. Clearance (in ml/min)
2. Wt (kg)
3. R (no. units, this line represent the point of reference)
4. Age (in year)
5. Serum creatinine (in mg/100 ml)

- The vertical line labeled "age" is marked separately for males and females, the markings on right side of this line are for females and markings on left side are for males.

- The nomogram is used as follow:

- Draw a straight line to connect patient's w (on the second line from left) to the patient' age (on the second line from right). This gives a point of intersection on the middle line R.

- Draw a stright line to connect the patient's serum creatinine value (on the 1st line on right to the point of intersection on line R) and extrapoluted this straight line to the 1st line on left to read creatinine clearance.

2. Traub And Johnson:

- This method uses a nomogram which requires the height and serum creatinine concentration of the patient.

- This nomogram consists of 3 vertical straight lines drawn to parallel to each other and at

Suitable distance.

- These straight line are as follows:

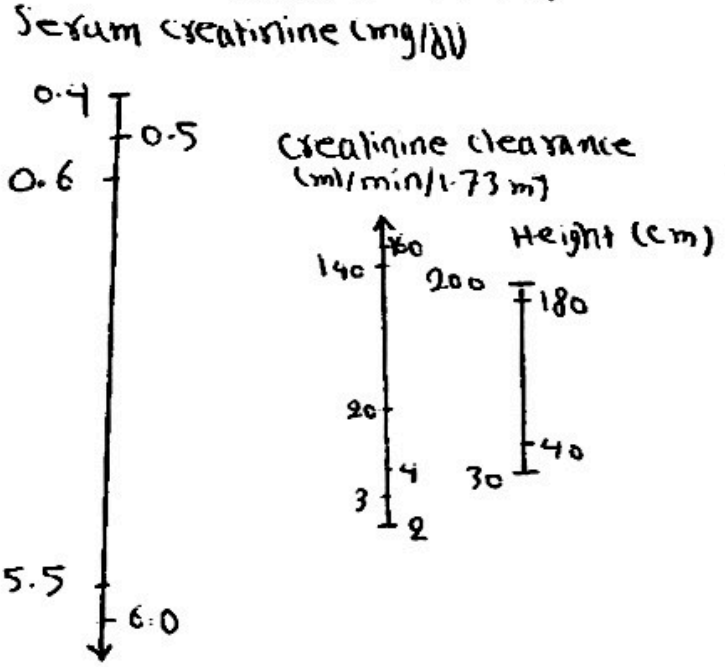
1. The vertical lines on the left represents serum creatinine concentration. This straight line is subdivided into units expressing serum creatinine concentration in mg/100 ml.

2. The vertical line on right represents height. This straight line is subdivided into units height of the child in centimeters.

3. The vertical line in the middle of these two lines represents creatinine clearance. This straight line is subdivided into units and expresses creatinine clearance in ml/min/1.73 m^2

- This method for determination of creatinine

clearance of child does not take into consideration the age or weight of the patient. It means this method will yield the same creatinine for all children regardless of their age or weight as long as these children have same height and same serum creatinine concentration.



-The nomogram developed by Traub and Johnson is used as follows:

- Draw a straight line to connect the patient's

serum creatinine value (in mg/100 ml to the patient's height (in cm).

• The point of intersection of this straight line and the vertical line in the middle of the nomogram indicates creatinine clearance of the patient in ml/min/1.73 m^2.

Advantages of Nomograms:

- Is that it can be easily mass-produced, distributed and evaluated, while providing the same information as the logistic regression it represent.

□ Tabulation:

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patients, including loading and maintenance doses.

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- Another example is the aminoglycoside antibiotic, tobramycin sulfate USP, which is eliminated primarily by renal clearance. Thus, the dosage of tobramycin sulfate should be reduced in direct proportion to a reduction in creatinine clearance.
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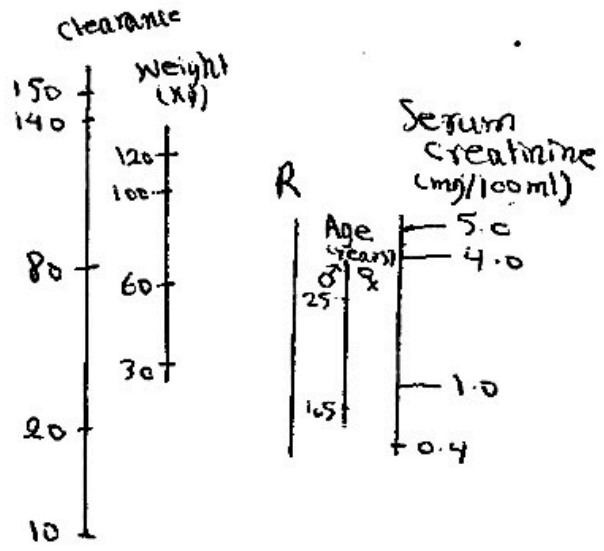

1. What are nomogram? [2M, Aug10

2. Explain the application of Nomograms. [2M, Feb11/12]

3. Enumerate the different methods of designing dosage regimens. [2M, Feb11]

4. Write the use of nomograms in ph.k. [2M, Aug11]

5. How do you determine dose for a drug [2M, 11]

6. Define and discuss the applications of nomograms [5M, 12]

7. Write briefly on different methods of designing dosage regimens. [2M, 12]

8. What are nomograms and explain their use in clinical pharmacokinetics + Exs [5M, 13]