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Calculating drug dosage, creatinine clearance and enteral-parenteral nutrition

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Many rules for drug dosage calculation have been developed based on body surface area, body weight and age; similarly rules for creatinine clearance have been described by different researcher, and the standards for calculating enteral and parenteral nutrition have been highlighted. But many rules are not simple enough to be used as such in routine practice. Among all these, the clinically result oriented rules and standards have been discussed and at the same time limitations have been mentioned.

Keyword: Drug dosage, Creatinine clearance, enteral nutrition, parenteral nutrition.

1. General Dose Calculation

1.1. Pediatric and Geriatric Patient Considerations

The important considerations in proper pediatric drug dosing and safe use of medications include patient's age, weight, health status; physiological considerations such as respiration and circulation, stage of body development of body system for metabolism and elimination. So the pharmacokinetic data and individual patient drug-handling features and therapeutic response must be use together to reach a rational approach of drug dosing [1].

The human physiological functions peak before thirty years of age, and show linear decline above 30 years [2]. So like pediatric patients, pharmacokinetic parameters are also important in geriatric patients in dosing of some selected drugs [3].

1.1.1. Dose calculation based on body weight.

Expressed as amount of drug/body weight, such as mg or mcg/kg; dose calculation on the basis of body weight can be used for both pediatric and geriatric patients. A useful equation in this regard is [4]:

Patient's dose (mg) = patient's weight (kg) x drug dose (mg)/1kg. (Units can be adjusted accordingly)

1.1.2. Dose calculation based on body surface area.

Body surface area (BSA) can be used for two types of patient groups:

1. Cancer patients with chemotherapy.
2. Pediatric patients, but not including neonates, because neonates are usually dosed based on body weight with physiological, pathological and immunological considerations [1].

The BNF and many other reference text books like Martindale recommend dosage calculation according to BSA in children [5]; because total dose is not directly proportional to the body weight but is more precisely proportional to BSA [6].

A useful equation in this regard is below [4].
Patient's dose = patient's BSA (m^2) / 1.73 m^2
The BSA can be calculated either

- By using available readymade Nomograms for BSA [7] or
- By using Mosteller equation (1987) [8], as below

Patient's BSA (m^2) = √patient's height (cm) x patient's weight (kg) / 3600
(Note: For pediatric patients medication doses, (either administered orally or parentally) must be carefully determined from available reference sources).
Rules for drug dosage have been developed on the basis of age, weight and body surface, it is generally recognized that dose requirements per unit of body weight are usually higher for children than for adults; Consequently the total dose is not directly proportional to the body weight, but appears to be more nearly proportional to the body surface area [9], so the most reliable among these rules is the dose calculation based on body surface area. J.A. Lack [10] shown that none of all these rules has been accurate and simple enough for routine practice, and proposed a more accurate rule for dosage calculation in children i.e. up to 30 kg, a child's drug dose may be (wt. x 2)% of an adult dose; over 30 kg (wt. + 2)% of an adult dose.

2. Calculations Involving Enteral & Parenteral Nutrition (Tpn): Enteral nutrition is to providing nutritional support through tubes inserted into stomach or small intestine-in case of inability of patient to ingest nutrients through oral route [11]. Similarly parenteral nutrition is used for patients who are not able to get adequate nutrition by oral; patients like severely malnourished, critical illness, GIT malfunctioning, ineffective nourishment via enteral means, and those with renal or hepatic failure [12].

2.1. Nutritional requirements
Requirements for micro and macro nutrients vary with individual's age, gender, physical parameters, disease state and current status of nutrition [13]. Given below is a short and comprehensive description of basic nutritional requirements and calculations involved.

2.2. Fluid requirements
Generally a factor of 30 ml/kg, 15 ml/m^2, and 1 ml/kcal are the methods used to estimate patient's daily fluid requirements on the basis of weight, body surface area and kcal of nutrition requirements respectively.
Further
For adults daily fluid requirements are 2 to 3 liter/day.
For pediatric group daily requirement of fluid can be calculated as (Table 01) [14];

Table 1: Fluid requirement for pediatric group on the basis of different parameters

Parameter		Fluid requirement
01	On the basis of age: Neonates	120 to 180 ml/kg/day
	1 month to 1 year	150 ml/kg/day (not exceeding 200 ml/kg/day)
02	On the basis of body weight: Body weight less than 10 kg	100 ml / kg / day
	Body weight 10 to 20 kg	1000 ml + 50 ml/kg/day (if wt. exceeds 10 kg)
	Body weight more than 20 kg	1500 ml + 20 ml/kg/day (if wt. exceeds 20 kg)
03	On the basis of body surface area: m^2 x 1500 ml/day/m^2	X ml / day
04	On the basis of daily caloric requirements: 1.2 ml/kcal x kcal/day	X ml / day

Above mentioned values may be decreased or increased on the basis of individual factors e.g. in renal failure, congestive heart failure and dehydration.

2.3. Caloric requirements

Caloric requirements depend on one's physical state and medical condition. For estimation of resting energy expenditure (REE (kcal/ 24 hours)) Harris Benedict equation is used [15].

For males:
REE = 66.67 + [13.75 x wt. (kg)] + [5 x height (cm)] – [6.76 x age (years)]

For females
REE = 655.1 + [9.56 x wt. (kg)] + [1.86 x height (cm)] – [4.68 x age (years)]
But in elderly patients REE determination by above Harris Benedict equation has been questioned recently and the following equation has been developed for elderly patients over 60 years of age [16].

For men
REE = [8.8 x wt. (kg)] + [1128 x height (m)] – 1071

For women
REE = [9.2 x wt. (kg)] + [637 x height (m)] – 302
Similarly as we know body composition vary with age, so the nutritional requirements for pediatric would be different from that of adults i.e. REE in pediatric population will be higher because of high metabolic rates. For children less than 3 years of age a modified form of Harris Benedict equation has been used developed by Callwell - Kennedy [17, 18].
REE = 22 + (31 x wt. in kg) + (1.2 x height in cm)
For estimation of resting energy expenditure (REE (kcal/ 24 hours)) Harris Benedict equation can be used effectively for most patients; but studies had been shown that, patients with severe illness, the Harris Benedict equation and related formulas couldn't accurately predicted REE [19, 20, 21, 22, 23] and indirect calorimetry for predicting energy requirements is more standardized technique [19, 24, 25]; other best methods for severely ill patients had also been described [26].

2.4. Carbohydrate requirements: In parenteral nutrition preparations, dextrose provides 3.4 kcal of energy/gram and for enteral nutrition, the factor 4 kcal/gram is used [27].
Dextrose is best one in parenteral nutrition because it's well absorbed and some patients show intolerance to lactose [28, 29]. Studies had been shown that the over administration of parenteral glucose may lead to systemic complications hepatic dysfunction, over production of carbon dioxide etc. [30, 24, 22, 25, 31] [32]. When administered intravenously the amount of glucose should not exceed 5-7 mg/kg/min; if the quantity exceeds this limit the patients wouldn't be able to oxidize it [33], and the total daily quantity should not exceed 300 to 4oo gram in average sized patients [30].

2.5. Protein requirements [12, 34]

Daily protein requirements for adults:

- 0.8 g/kg/day in an unstressed patient.
- 0.8 to 1 g/kg for mildly stressed patient.
- 0.8 to 1.2 g/kg for a renal dialysis patient.
- 1.1 to 1.5 g/kg for moderately stressed patient
- 1.5 to 2 g/kg for severely stressed patient / critical illness / trauma.
- 3 g/kg for severely burned patients.
  For infants:
- 2 to 3 g/kg/day
  For children:
- 1.5 to 2 g/kg/day
  For teen agers:
- 1 to 1.5 g/kg/day

The over administration of protein can lead to severe ureagenesis and similarly insufficient administration can cause persistent nitrogen wastage, both of which can cause severe damage [25, 35, 36]. Generally 1.5 to 2 g/kg/day of protein had been proven appropriate for most of the patients [37, 30, 35, 38, 39]. Preparations containing high concentrations of Leucine, isoleucine and valine may increase protein synthesis and attain nitrogen balance even at low protein concentration and may be beneficial among patients with renal and hepatic diseases [40, 38]. Similarly glutamine and arginine rich preparations may act as respiratory fuel of the enterocytes and modulator of the immune system respectively [41, 42]. Studies had been suggested that simple protein sources rather than complex proteins are well tolerated by the patients [43, 37].

2.6. Lipid requirements

One can gain 9 kcal of energy per gram of lipids. Lipids are administered in emulsion form consists of carbohydrate based emulsifying agents, which also contains some calories. It has been determined that one can gain 11 kcal/g of total energy by using 10% lipids emulsion, and 10 kcal/g of total energy from 20 to 30% lipid emulsion [27, 44].

The over consumption of lipids in the form of long chain triglycerides may lead to immunological disorders [21, 45, 46]. Generally 20 to 30% lipid emulsions have been shown to be safe, when used intravenously [22, 45, 47]. Initially when enteral route is chosen, medium chain triglycerides are considered to be more appropriate source as compared to long chain triglycerides [38, 29, 45]; and once patient is tolerated (absorption), must be switch to long chain triglycerides sources because medium chain triglycerides does not contain essential fatty acids.

2.7. Fiber requirements

14 g of fiber/day for each 1000 calories consumed is recommended by guidelines; so this means that for men 30 to 38 g/day and for women 21 to 25 g/day fiber is recommended [48].

2.8. Micro Nutrients

For micronutrients, (electrolytes, vitamins, traces of elements like zinc etc.) standard quantities can be used in parenteral and enteral nutrition.

3. Calculating Creatinine Clearance rate

Creatinine clearance rate determines the normal kidney function, as many polar drugs eliminated though kidney, so impaired kidney function will affect the elimination and leads to systemic toxicity, so dosage adjustment in renal impairment must be done on the basis of creatinine clearance.

Normal adult value of serum creatinine = 0.7–1.5 mg/dl; units for creatinine clearance are ml/minute

3.1. By Cockcroft - Gault equation [49].

For males

$$CrCl = \frac{(140 - \text{patient's age in years}) \times \text{body wt. in kg}}{72 \times \text{serum creatinine in mg/dl}}$$

For females

$$CrCl = 0.85 \times \frac{[(140 - \text{patient's age in years}) \times \text{body wt. in kg}]}{72 \ \text{serum creatinine in mg/dl}}$$

3.2. By Jelliffe equation [50, 51].

For Males

$$CrCl = \frac{98 - 0.8 \times (\text{patient's age in years} - 20)}{\text{Serum creatinine in mg / dl}}$$

For Females

$$CrCl = 0.9 \times \frac{[98 - 0.8 \times (\text{patient's age in years} - 20)]}{\text{Serum creatinine in mg / dl}}$$

3.3. By Sanaka equation

For patients over 60 years of age [52]

For Males

$$CrCl = \frac{\text{patient's weight (kg)} \times [19 \times \text{plasma albumin (g / dl)} + 32]}{100 \times \text{serum creatinine (mg / dl)}}$$

For Females

$$CrCl = \frac{\text{patient's weight (kg)} \times [13 \times \text{plasma albumin (g / dl)} + 29]}{100 \ \text{serum creatinine (mg/dl)}}$$

3.4. Schwartz equation

For neonates and pediatric group to 17 years of age [52]

$$CrCl = \frac{k \times \text{patient's height (cm)}}{\text{Serum creatinine (mg/dl)}}$$

Where k = proportionality constant, value for neonates = 0.33 & for adolescent = 0.70.

3.5. Salazar-Corcoran equation [53]

For Men:

$$\frac{[137 - \text{age}] \times [(0.285 \times \text{weight(kg)}) + (12.1 \times \text{height (m) } 2)]}{(51 \times SCr)}$$

For Women:

$$\frac{[146 - \text{age}] \times [(0.287 \times \text{weight (kg)}) + (9.74 \times \text{height(m)}2)]}{(60 \times SCr)}$$

Spinler SA *et al.* [54] evaluated that among the different equations used for predicting Creatinine clearance the Salazar-Corcoran and Cockcroft-Gault appear to be the best. Use of the Cock craft-Gault and related equations requires stable kidney function and steady-state serum creatinine concentrations. The equations should be used cautiously in critically ill patients, individuals with acute kidney injury, and patients requiring renal replacement therapy. Factors that should be considered include the performance of the equation in the specific patient population; the therapeutic index, indication, and toxicity profile of the drug; availability of alternative agents; and whether the drug dosage can be titrated to response or dosed using serum concentrations and prospective pharmacokinetic methods; and it has been investigated that the Cockcroft-Gault and related equations derived kidney function estimate should not be used as the sole determinant of drug dosing decisions, and final decision should be taken on the basis of risk: benefit ratio of different approaches, keeping in view the patient's clinical profile [55].

4. Last Wordings

A clinical pharmacist providing pharmaceutical care in primary care centers, and specialized healthcare setups must be aware of basic and significant clinical calculations to reduce possible prescribing errors and adverse drug effects in order to optimize patient outcome without adversely affecting patient health; similarly physicians and consultants in coordination with clinical pharmacist as a healthcare team can plan a rational medication therapy; which will obviously increases therapeutic outcomes without adversely affect patient's health.

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