Variability in Drug Dosage Requirements

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Renal function

- When infants are born, renal function is not yet completely developed.

- Kidney development is complete and renal function stabilizes 3–6 months after birth.

- Kidney function, as measured by glomerular filtration rate, typically averages ~**120–140 mL/min** in young, healthy adults between the ages of 18–22 years.

Renal function

- As humans age, there is a gradual decline in glomerular function so that by 65 years of age, the average glomerular filtration rate is ~50–60 mL/min.

- The expected glomerular filtration rate for otherwise healthy, normal 80-year-old adults is ~30–40 mL/min.

- A glomerular filtration rate of 80–120 mL/min is usually considered the normal range by most clinical laboratories.

Renal disease

- Patients with **acute kidney failure** may get back their baseline renal function after a period of supportive care and dialysis, for example;
    - Hypotension, shock, or hypovolemia
    - Nephrotoxic drug therapy such as aminoglycoside or vancomycin
- Patients with **chronic renal failure** sustain permanent loss of functional nephrons due to irreversible damage and do not recover lost kidney function.

Measurement of creatinine clearance

- Most water-soluble drugs are eliminated unchanged to some extent by the kidney.

- Glomerular filtration is the primary elimination route for many medications.

- The method recommended by the Food and Drug Administration (FDA) and others to estimate renal function for the purposes of drug dosing is to measure or estimate creatinine clearance (CrCl).

Measurement of creatinine clearance

- Creatinine clearance rates can be measured by collecting urine for a specified period and collecting a blood sample for determination of serum creatinine at the midpoint of the concurrent urine collection time:

$$CrCl\ (ml/min) = (U_{Cr} \cdot V\ urine)/(S_{Cr} \cdot T)$$

U_{Cr}: urine creatinine concentration (mg/dL)

V urine: volume of urine collected (ml)

SCr: serum creatinine collected at the midpoint of the urine collection (mg/dL)

T : time of the urine collection (minutes)

Measurement of creatinine clearance

- Because creatinine renal secretion exhibits diurnal variation, most nephrologists use a 24-hour urine collection period for the determination of creatinine clearance.

Measurement of creatinine clearance

- For example, a 24-hour urine was collected for a patient with the following results:

U_{Cr} = 55 mg/dL

V urine = 1000 mL

S_{Cr} = 1.0 mg/dL

T = 24 h × 60 min/h =1440 min

CrCl (in mL/min) = $(U_{Cr} \cdot V \text{ urine})/(S_{Cr} \cdot T)$

= (55 mg/dL · 1000 mL) /(1.0 mg/dL · 1440 min)

= 38 mL/min

Measurement of creatinine clearance

- However, for the purpose of drug dosing, collection periods of 8–12 hours have been sufficient.

- Inaddition, if renal function is stable, the blood sample for determination of serum creatinine may not need to be collected at the precise midpoint of the urine collection.

Measurement of creatinine clearance

- Routine measurement of creatinine clearances has been associated with several problems:
    - *Incomplete urine collections*
    - *Serum creatinine concentrations obtained at incorrect times*
    - *Collection time errors*

Estimation of creatinine clearance

- The most widely used of these formulas for adults aged 18 years and older is the method suggested by ***Cockcroft and Gault:***

Estimation of creatinine clearance

- For males,

$$CrCl_{est} = [(140 - age)\ BW] / (72 \cdot S_{Cr})$$

- For females,

$$CrCl_{est} = [0.85(140 - age)BW] / (72 \cdot S_{Cr})$$

- The 0.85 correction factor for females is present because women have smaller muscle mass than men and, therefore, produce less creatinine per day.

$CrCl_{est}$: estimated creatinine clearance (mL/min)
Age (years)
BW: body weight (kg)
S_{Cr}: serum creatinine (mg/dL)

Estimation of creatinine clearance

- The Cockcroft-Gault method should only be used in patients:
  - *≥18 years old*
  - *Actual weight within 30% of their ideal body weight*
  - *Stable serum creatinine concentrations*

- Ideal body weight

IBW males (kg) = 50 + 2.3(Ht – 60)

IBW females (kg) = 45 + 2.3(Ht - 60)

Ht: height in inches

Estimation of creatinine clearance

- For example, A 55-year-old, 80-kg, 5-ft 11-in male has a Scr 1.9 mg/dL.

IBW males = 50 + 2.3 (Ht - 60) = 50 + 2.3(71 - 60) = 75 kg

so the patient is within 30% of his ideal body weight

the Cockcroft-Gault method can be used;

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr})$$
$$= [(140 - 55\ y)80\ kg] / (72 \cdot 1.9\ mg/dL)$$
$$= 50\ mL/min$$

Estimation of creatinine clearance

- Patients with spinal cord injury, cancer patients with muscle wasting, HIV-infected patients and patients with poor nutrition are examples of situations where ***muscle mass*** may be very small resulting in ***low creatinine production***.

- In these cases, serum creatinine concentrations are low because of the low creatinine production rate and not due to high renal clearance of creatinine.

Estimation of creatinine clearance

- In these cases, investigators have suggested that if serum creatinine values are <1.0 mg/dL for a patient an arbitrary value of 1 mg/dL be used in the Cockcroft-Gault formula to estimate creatinine clearance.

It may be necessary to measure creatinine clearance in these types of patients if an accurate reflection of glomerular filtration rate is needed

Estimation of creatinine clearance

- If serum creatinine values are not stable, the Cockcroft-Gault equation cannot be used to estimate creatinine clearance.

- In this case, an alternate method must be used which is ***Jelliffe and Jelliffe***

Ess male = IBW[29.3 - (0.203 · age)]

Ess female = IBW[25.1 - (0.175 · age)]

Ess: excretion of creatinine

IBW: ideal body weight (kg)

Age (years)

Estimation of creatinine clearance

$$Ess_{corrected} = Ess\ [1.035 - (0.0337 \cdot Scr_{ave})]$$

$$E = Ess_{corrected} - \frac{[4IBW(Scr_2 - Scr_1)]}{\Delta t}$$

$$CrCl\ (in\ mL/min\ /\ 1.73m^2) = E/(14.4 \cdot Scr_{ave})$$

Scr_{ave}: average of the two serum creatinine determinations in mg/dL
Scr_1: first serum creatinine (mg/dL)
$Scr_{2:}$ second serum creatinine (mg/dL)
Δt: time that expired between the measurement of Scr_1 and Scr_2 (minutes)

Estimation of creatinine clearance

- If patients are not within 30% of their ideal body weight, we can use the ideal body weight or adjusted body weight (ideal body weight plus 40% of obese weight) in the Cockcroft-Gault equation for obese individuals.

Estimation of creatinine clearance

- However, a specific method (*Salazar and Corcoran*) for estimating creatinine clearance for obese patients:

$$\mathrm{CrCl_{est}\ (males)} = \frac{(137 - \mathrm{age})[(0.285 \cdot \mathrm{Wt}) + (12.1 \cdot \mathrm{Ht}^2)]}{(51 \cdot \mathrm{Scr})}$$

$$\mathrm{CrCl_{est}\ (females)} = \frac{(146 - \mathrm{age})[(0.287 \cdot \mathrm{Wt}) + (9.74 \cdot \mathrm{Ht}^2)]}{(60 \cdot \mathrm{Scr})}$$

Wt: weight (kg)
Ht: height (m)
S_{Cr}: serum creatinine (mg/dL)

Estimation of creatinine clearance

- Methods to estimate creatinine clearance for children and young adults are also available according to their age:

age 0–1 year,

CrCl est (in mL/min /1.73 m^2) = (0.45 · Ht)/SCr

age 1–20 years,

CrCl est (in mL/min /1.73 m^2) = (0.55 · Ht)/SCr

Ht: height (cm)

SCr: serum creatinine (mg/dL)

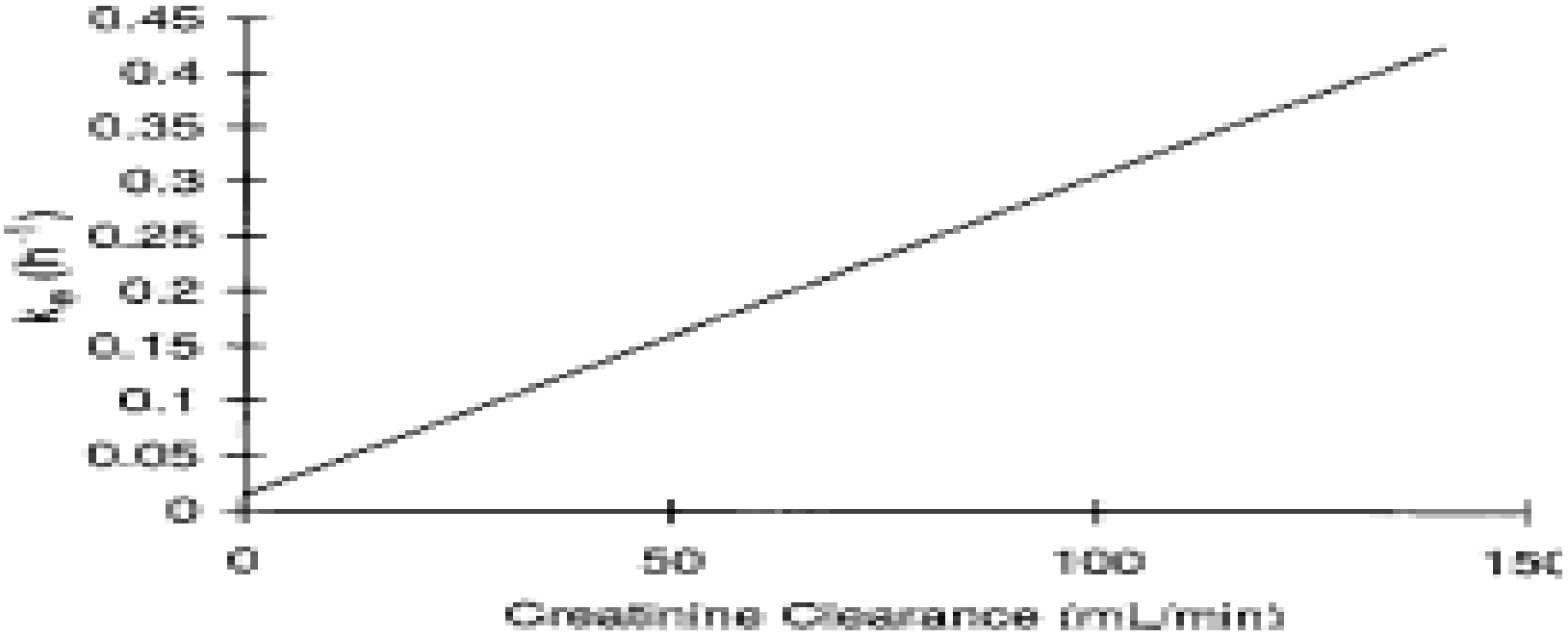
Estimation of drug dosing using creatinine clearance

- In order to modify doses for patients with renal impairment, it is possible;
  - **Decrease the drug dose and retain the usual dosage interval**
  - **Retain the usual dose and increase the dosage interval**
  - **Simultaneously decrease the dosage and prolong the dosage interval**

Estimation of drug dosing using creatinine clearance

- ***Creatinine clearance*** may be used to estimate pharmacokinetic parameters for a patient based on prior studies conducted in other patients with renal dysfunction.

- Estimated pharmacokinetic parameters are then used in pharmacokinetic dosing equations to compute initial doses for patients.



Relationship between Clcr and aminoglycoside elimination rate constant (Ke) used to estimate initial aminoglycoside elimination when no drug concentration are avialble. The y-axis intercept (0.014 h) is nonrenal elimination for aminoglycosides.

Estimation of drug dosing using creatinine clearance

$$ke\ (h^{-1}) = 0.00293 \cdot CrCl + 0.014$$

Estimation of drug dosing using creatinine clearance

- Volume of distribution can also change in patients with decreased renal function.

- **Plasma protein binding displacement** of drug by endogenous or exogenous substances accumulate in the blood of patients with poor kidney function can ***increase*** the volume of distribution of drugs.

- Conversely, the volume of distribution of a drug can ***decrease*** if compounds normally excreted by the kidney accumulate to the extent that displacement of drug from tissue binding sites occurs.

Estimation of drug dosing using creatinine clearance

- Digoxin volume of distribution decreases in patients with decreased renal function;

$$V \text{ (in L)} = 226 + [(298 \cdot CrCl)/(29.1 + CrCl)]$$

- The decline in volume of distribution presumably occurs because of displacement of tissue-bound digoxin.

Hepatic disease

- Most lipid-soluble drugs are metabolized to some degree by the liver.

- When infants are born, hepatic metabolism of drugs is not completely developed but it continues to increase so that by age 3–6 months it is stable.

- On a per kilogram basis, drug metabolism is more rapid in children until puberty.

Hepatic disease

- At that point, metabolic rate gradually decreases to adult values.
- The effect of advanced age on hepatic drug metabolism is quite variable.
- Patients over the age of 65 years may have decreased hepatic clearance of some drugs.

Hepatic disease

- There are two major types of liver disease:
  - ***hepatitis***
  - ***cirrhosis***
- Patients with ***acute hepatitis*** usually experience mild, transient decreases in drug metabolism that require ***no or minor changes in drug dosing.***

Hepatic disease

- If the patient develops ***chronic hepatitis***, it is likely that irreversible hepatocyte damage will be more widespread, and drug dosage changes will be required at some point.

- In patients with ***hepatic cirrhosis***, there is a permanent loss of functional hepatocytes.

- Drug dosage schedules usually need to be modified in patients with severe cirrhosis.

Hepatic disease

- If the drug experiences a hepatic first-pass effect, less drug will be lost by presystemic metabolism and bioavailability will increase.

- A simultaneous decrease in hepatic clearance and liver first-pass effect results in extremely large increases in steady-state concentrations for orally administered drugs.

Hepatic disease

- Liver blood flow also decreases in patients with cirrhosis.

- The decrease in liver blood flow results in less drug delivery to still-functioning hepatocytes and depresses hepatic drug clearance even further.

Hepatic disease

- The liver produces albumin and α-1-acid glycoprotein, the two major proteins that bind acidic and basic drugs, respectively, in the blood.

- In patients with cirrhosis, the production of these proteins decline.

- When this is the case, the free fraction of drugs in the blood increases because of a lack of binding proteins.

- Additionally, high concentrations of endogenous substances in the blood that are normally eliminated by the liver, such as bilirubin, can displace drugs from plasma protein binding sites.

Thank You