Pharmacokinetics 31. **11-24-2008**

Dosage Adjustment in Renal Disease I

❶ Uremia and Pharmacokinetics

❷ Assessment of Renal Function
--- Clearance Measurements
--- Estimates Using Empirical Relationships

❸ Determination of the Elimination Rate Constant in Uremia

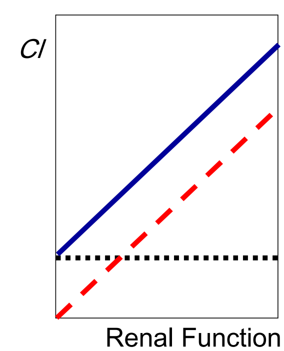
Uremia

- common description for accumulation of excessive fluid and nitrogenous metabolic waste in the body elicited by impaired or reduced glomerular filtration
- causes
  --- injury of kidney
  --- disease (pyelonephritis, hypertension, diabetes)
  --- nephrotoxic drugs taken long-term (aminoglycosides, phenacetin)
  --- heavy metals (lead, mercury)

Uremia and Drug Effects

- predominant influence - decrease of renal excretion, but other influences possible
- changes in pharmacodynamics, in both therapeutic and toxic responses
- oral bioavailability may be
  --- decreased due to lower GI motility and pH
  --- increased due to lower first-pass effect
- plasma protein binding decreased especially for acidic drugs

- clearance:
  renal
  and nonrenal
  components
- only the renal component depends on renal function
- renal function assessed as clearance of inulin or creatinine



Measurement of Glomerular Filtration Rate (GFR)

Criteria for markers used for measurement of GFR:

- free glomerular filtration = no plasma protein binding
- no active tubular secretion, no reabsorption
- no metabolism
- low toxicity permitting high dosing (if needed)
- accurate determination in urine and plasma

Measurement of GFR by Inulin

- inulin – linear fructose polysaccharide
- given by IV infusion
- at the steady state the plasma concentration c_{SS} is determined
- clearance is calculated from

$$c_{SS} = \frac{R}{k_e \times V_D} = \frac{R}{Cl}$$

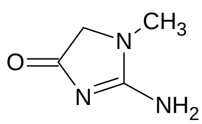
as

$$Cl = \frac{R}{c_{SS}} \quad (1)$$

- inulin clearance - accurate, but not frequently used due to discomfort and cost

Creatinine

- creatinine - endogenous substance (no dosing)
- chemical name 2-amino-1-methyl-imidazolidin-4-one


(pK_a=4.4)

- formed during muscle metabolism - rate of production depends on factors like
  --- age, weight, gender
  --- muscle atrophy (false negatives)
  --- large intake of (fried) meat (false positives)

GFR by Creatinine

- creatinine - endogenous substance (no dosing)
- formed during muscle metabolism - rate of production depends on age, weight, and gender
- mainly filtered at glomerulus, but small tubular active secretion may occur - clearance higher than inulin clearance
- clearance can be
  --- determined using serum and urine creatinine concentrations (method I)
  --- estimated using serum creatinine concentration alone (method II)

Determination of GFR by Creatinine - Method I

- urine creatinine concentration needs to be determined for the entire day (reliability)
- serum creatinine concentration is usually determined in the middle of the urine collection period (AUC/Δt would be more precise)
- then

$$Cl_{Cr} = \frac{\text{rate of urinary excretion}}{\text{plasma concentration}} \quad (2)$$

Estimation of GFR by Creatinine - Methods II: Adults (20+ Years of Age)

- plasma concentration of creatinine (c_{Cr} in mg/dL) is routinely measured in the clinical laboratory
- for persons with the average muscle/fat ratio (Cl_{Cr} in mL/min, weight in kg)
- Jellife, 1973, for males: females 90%

$$Cl_{Cr} = \frac{98 - 0.8 \times (\text{Age} - 20)}{c_{Cr}} \quad (3)$$

- Cockroft and Gault, 1976, females 85%

$$Cl_{Cr} = \frac{(140 - \text{Age}) \times \text{Weight}}{72 \times c_{Cr}} \quad (4)$$

Estimation of GFR by Creatinine - Methods II: Children (1 - 19 Years of Age)

- height in cm, weight in kg, c_{Cr} in mg/dL, Cl_{Cr} in mL/min
- Schwartz *et al*, 1976

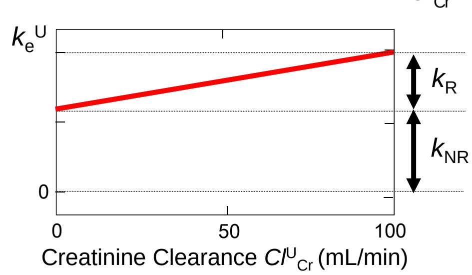
$$Cl_{Cr} = \frac{0.55 \times \text{Height}}{c_{Cr}} \quad (5)$$

- Traub & Johnson, 1980 modified by Rowland & Tozer

$$Cl_{Cr} = \frac{0.48 \times \text{Height}}{c_{Cr}} \times \left(\frac{\text{Weight}}{70}\right)^{0.7} \quad (6)$$

Elimination Rate Constant in Uremia II

$$k_e^U = k_{NR} + \alpha \times Cl_{Cr}^U \qquad k_e^U = k_{NR} + k_R^N \times \frac{Cl_{Cr}^U}{Cl_{Cr}^N}$$



Elimination Rate Constant in Uremia III

The elimination rate constant k_e has to be divided into renal and nonrenal components $\alpha = \frac{k_R^N}{Cl_{Cr}^N}$

- if k_{NR} and k_e are published $$\alpha = \frac{k_e - k_{NR}}{Cl_{Cr}^N} \quad (10)$$
- if k_e and fraction of drug excreted unchanged (f_e) are published
  Giusti-Hayton method $f_e = \frac{k_R^N}{k_e}$; $k_R^N = f_e \times k_e$
  $$\alpha = \frac{f_e \times k_e}{Cl_{Cr}^N} \quad (11)$$

Practice Problem 31.1

A patient (6'3", 85 kg, 47 years) has plasma creatinine concentration 1.6 mg/dL. Determine the percentage of remaining renal function if the patient is

1. man (assume normal Cl_{Cr} = 108 mL/min)
2. woman (assume normal Cl_{Cr} = 97 mL/min).

Eq. 4

Practice Problem 31.2

A woman (5'10", 60 kg, 35 years) is taking 200 mg of a drug every 8 hours. The drug has fast absorption, fast plasma/tissue distribution, and is eliminated by renal excretion and hepatic metabolism. Under normal conditions, the rates of excretion and metabolism are equal and the elimination rate constant is k_e = 0.1 hr^{-1}. Plasma creatinine concentration of the patient has increased from the normal value of 0.9 mg/dL to 1.4 mg/dL. How would you adjust her dosing interval to maintain the same maximum drug level as under normal conditions? Eqs. 4, 8, 11

Practice Problem 31.3

A patient (5'0", 50 kg, 15 years) is taking 100 mg of a drug every 8 hours. The drug has fast absorption, fast plasma/tissue distribution, and is eliminated by renal excretion and hepatic metabolism. Under normal conditions, the rates of excretion and metabolism are 2:1 and the elimination rate constant is k_e = 0.12 hr^{-1}. Plasma creatinine concentration of the patient has increased from the normal value of 1 mg/dL to 1.3 mg/dL. How would you adjust the dosing interval to maintain the same maximum drug level as under normal conditions? Eqs. 6, 8, 11