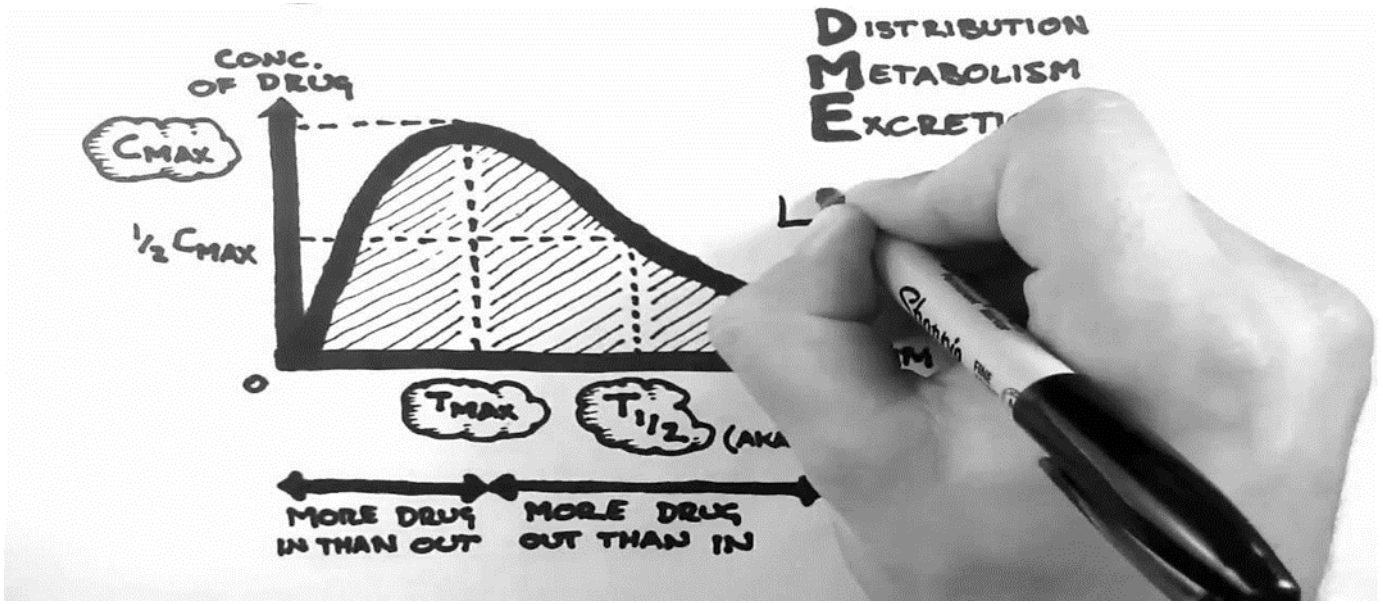
TDM/CH 3



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DRUG DOSING IN SPECIAL POPULATIONS: RENALAND HEPATIC DISEASE, DIALYSIS, HEART FAILURE, OBESITY, AND DRUG INTERACTIONS

Effect of renal diseases on PK parameters

- **Measurement of GFR using MDRD;**

GFR (mL/min/1.73 m^2) = 186.Scr $^{-1.154}$.Age $^{-0.203}$.0.742 (if female).1.21 (for African-American)

- **Measurement and estimation of renal diseases:**

Method 1

Most appropriate method because it concentrate between Scr and Ucr;

$$CrCl\left(\frac{mL}{\min}\right) = \frac{Ucr.Vu}{Scr.T\,u}$$

Method 2 (cock croft and gault method)

1. **Pt must be older than 18 years.**
2. **Pt must ne not obese (ABW within 30% of IBW)**
3. **stable Scr concentration**

for males, **CrClest = [(140 − age)BW]/ (72 · SCr)**

for females, **CrClest = [0.85(140 − age)BW] / (72 · SCr)**

$$\%\,overweight = \frac{ABW - IBW}{IBW}.100$$

$$\text{IBW males (in kg)} = 50 + 2.3(\text{Ht} - 60)$$

$$\text{IBW females (in kg)} = 45 + 2.3(\text{Ht} - 60)$$

Method 3 (jelliffe and jelliffe method) Used if Scr concentration unstable

- Estimate creatinine production;

$$\text{Ess male} = \text{IBW}[29.3 - (0.203 \cdot \text{age})]$$

$$\text{Ess female} = \text{IBW}[25.1 - (0.175 \cdot \text{age})]$$

- Correct creatinine production for renal function,

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

- Adjust the estimated creatinine clearance value

$$E\ adjusted\ =\ E\ ss\ corrected - \frac{4\ IBW Scr1 - Scr2}{\Delta t}$$

$$\text{CrCl (in mL/min / 1.73m2)} = \text{E}/(14.4 \cdot \text{Scr ave})$$

Method 4 (Salazar and Corcoran method)

1. **Pt must be older than 18 years.**
2. **obese Pt**
3. **stable Scr concentration**

$$CrCl\ (male) = \frac{(137 - age)[(0.285\ wt) + (12.1\text{Ht}^2)]}{51 Scr}$$

$$CrCl\ (female) = \frac{(146 - age)[(0.287\ wt) + (9.74\text{Ht}^2)]}{60\ Scr}$$

Method 5

Used to estimate CrCl in young adult and children;

age 0–1 year, CrClest (in mL/min / 1.73 m2) = (0.45 · Ht) / SCr

age 1–20 years, CrClest (in mL/min / 1.73 m2) = (0.55 · Ht)/SCr

Q1. A creatinine clearance is measured in a 75-year-old Caucasian male patient with multiple myeloma to monitor changes in renal function. The serum creatinine, measured at the midpoint of the 24 hour urine collection, was 2.1 mg/dL. Urine creatinine concentration was 50 mg/dL, and urine volume was 1400 mL. (A). Calculate this patient's creatinine clearance. (B). Estimate the patient's glomerular filtration rate using the modified MDRD equation.

Answer;

Age = 75 year, Scr = 2.1 mg/dL, T = 24 h, Ucr = 50 mg/dL, V urine = 1400 mL

A)

$$CrCl\ (ml/min) = \frac{Ucr.Vu}{Scr.T\ u}$$

$$CrCl\ (mL/min) = \frac{50mg/dL * 1400\ mL}{2.1\frac{mg}{dL} *\ \ (24\ * 60min)}$$

$$CrCl\ (mL/min) = 23\ mL/min$$

B) **GFR (mL/min/1.73 m^2) = 186.Scr $^{-1.154}$.Age $^{-0.203}$**

GFR (mL/min/1.73 m^2) = 186. (2.1 mg/dL) $^{-1.154}$.(75 $^{-0.203}$)

GFR= 33 mL/min/1.73 m^2

Q2. A 52-year-old, 65-kg, 5-ft 3-in tall female patient with a methicillin-resistant Staphylococcus aureus (MRSA) infection needs to have an initial vancomycin dose computed. In order to do this, an estimated creatinine clearance needs to be calculated. The patient has a serum creatinine value equal to 1.8 mg/dL. Calculate this patient's estimated creatinine clearance and estimated vancomycin clearance [assume vancomycin clearance is Cl (in mL/min/kg) = 0.695 (CrCl in mL/min/kg) + 0.05].

Answer;
Age = 52 year, wt = 65 kg, Ht = 5 ft 3 in(5*12 in+ 3 in) = 63 in,
Scr = 1.8 mg/dL, CrCl = ?, vancomycin Cl=?

IBW females (in kg) = 45 + 2.3(Ht − 60)
IBW females (in kg) = 45 + 2.3(63 − 60)
IBW females (in kg) =52 kg

$$\%\ overweight\ = \frac{ABW - IBW}{IBW}.100$$

$$\%\ overweight\ = \frac{65 - 52}{52}.100$$

$$\%\ overweight\ = 25\%$$

Patient’s estimated creatinine clearance;

$$\text{CrCl est} = [0.85(140 - \text{age})\text{BW}] / (72 \cdot \text{SCr})$$

$$\text{CrCl est} = [0.85(140 - 52)65] / (72 \cdot 1.8)$$

CrCl est =37 mL/min for 65 kg

CrCl est =37 mL/min/ 65 kg

CrCl est =0.569 mL/min /kg

Estimated vancomycin clearance;

$$\text{Cl (in mL/min/kg)} = 0.695\ (\text{CrCl in mL/min/kg}) + 0.05$$

$$\text{Cl (in mL/min/kg)} = 0.695\ (0.569) + 0.05$$

Cl (in mL/min/kg) = 0.445 mL/min/kg

Cl (in mL/min/kg) = 29 mL/min

Q3. A 70-year-old, 80-kg, 5-ft 11-in tall male with a Pseudomonas aeruginosa infection needs to have an initial tobramycin dose computed. In order to do this, an estimated creatinine clearance must be calculated. The patient's current serum creatinine equals 2.5 mg/dL and is stable. Compute this patient's estimated creatinine clearance and estimated tobramycin elimination rate constant and half-life [assume tobramycin elimination rate constant is ke (in h−1) = 0.00293 (CrCl in mL/min) + 0.014].

Answer;

Age = 70 year, wt = 80 kg, Ht = 5 ft 11 in (5*12 in +11 in= 71 in),

CrCl=?, Scr = 2.5 mg/dL, Ke=?

IBW male (in kg) = 50 + 2.3(71 − 60)

IBW male (in kg) = 50 + 2.3(71 − 60)

IBW male (in kg) =75 kg

$$\%\ overweight\ = \frac{ABW - IBW}{IBW}.100$$

$$\%\ overweight\ = \frac{80 - 75}{75}.100$$

$$\%\ overweight\ = 22.5\%$$

Patient’s estimated creatinine clearance;

$$\text{CrCl est} = [(140 - \text{age})\text{BW}]/ (72 \cdot \text{SCr})$$

$$\text{CrCl est} = [(140 - 70)80] / (72 * 2.5)$$

$$\text{CrCl est} = 31 \text{ mL/min for } 80 \text{ kg}$$

$$\text{CrCl est} = 31 \text{ mL/min/ } 80 \text{ kg}$$

$$\text{CrCl est} = 0.388 \text{ mL/min /kg}$$

estimated tobramycin elimination rate constant and half-life

$$\mathbf{ke \text{ (in } h^{-1}\text{)} = 0.00293 (31) + 0.014}$$

$$\mathbf{ke = 0.105\ h^{-1}}$$

$$\mathbf{t_{1/2} = 0.693/Ke}$$

$$\mathbf{t_{1/2} = 0.693/0.104}$$

$$\mathbf{t_{1/2} = 6.6\ h}$$

Q4. A 51-year-old, 54-kg, 5-ft 4-in female with worsening renal function needs to have her renal function assessed for drug dosage adjustment. Yesterday, at 0800 H, her serum creatinine was 1.3 mg/dL. Today at 0800 H, her serum creatinine was 2.1 mg/dL. Compute her estimated creatinine clearance.

Answer;

Age = 51 year, Ht = 5 ft 4 in (5 *12in +4 in= 64 in),

Scr 1 = 1.3 mg/dL at morning of first day,

Scr 2 = 2.1 mg/dL at morning of second day,

$$\text{IBW females (in kg)} = 45 + 2.3(\text{Ht} - 60)$$

$$\text{IBW females (in kg)} = 45 + 2.3(64 - 60)$$

$$\text{IBW females (in kg)} = 54 \text{ kg}$$

Estimate creatinine production;

$$\text{Ess female} = \text{IBW}[25.1 - (0.175 \cdot \text{age})]$$

$$\text{Ess female} = 54[25.1 - (0.175 \cdot 51)]$$

$$\text{Ess female} = 873.5$$

Correct creatinine production for renal function,

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

$$\text{Ess corrected} = 873.5[1.035 - (0.0337 \cdot 1.7)]$$

$$\text{Ess corrected} = 854$$

Adjust the estimated creatinine clearance value

$$E\ adjusted\ =\ E\ ss\ corrected\ -\ \frac{4\ IBW\ (Scr1-Scr2)}{\Delta t}$$

$$E\ adjusted\ = 854 -\ \frac{4\ *54(2.1-1.3)}{24*60\ min}$$

$$E\ adjusted\ = 853.9$$

CrCl (in mL/min / 1.73m2) = E/(14.4 · Scr ave)

CrCl (in mL/min / 1.73m2) = 853.1/(14.4 *1.7)

CrCl = 35 mL/min / 1.73m2

Q5. A 66-year-old, 120-kg, 5-ft 2-in tall female has a serum creatinine equal to 3.1 mg/dL. Compute an estimated creatinine clearance for this patient.

Answer;

Age = 66 year, wt = 120 kg, Ht = 5 ft 2 in (5*12in +2 in = 62 in),

Scr = 3.1 mg/dL, CrCl=?

IBW females (in kg) = 45 + 2.3(Ht − 60)

IBW females (in kg) = 45 + 2.3(62 − 60)

IBW females (in kg) =50 kg

$$\%\ overweight\ = \frac{ABW - IBW}{IBW}.100$$

$$\%\ overweight\ = \frac{120 - 50}{50}.100$$

$$\%\ overweight\ = 33\%$$

$$CrCl\ (female) = \frac{(146 - age)[(0.287\ wt) + (9.74\text{Ht}^2\ )]}{60\ Scr}$$

$$CrCl\ (female) = \frac{(146 - 66)[(0.287 * 120) + (9.74\ * 1.57^2\ m)]}{60\ * 5.1}$$

$$CrCl\ (female) = 25\ mL/min$$

Q6. A 59-year-old, 140-kg, 5-ft 8-in tall male with severe heart failure has a serum creatinine equal to 2.4 mg/dL. Compute an estimated creatinine clearance, digoxin clearance, and digoxin volume of distribution for this patient. Assume estimated digoxin clearance in severe heart failure: Cl (in mL/min) = 1.303 (CrCl in mL/min) + 20; estimated digoxin volume of distribution: V (in L) = 226 + [(298 · CrCl)/ (29.1 + CrCl)].

Answer;
Age = 59 year, wt = 140 kg, Ht = 5 ft 8 in (5*12in +8 in = 68 in),
Scr = 2.4 mg/dL, CrCl =?, digoxin Cl =?, V=?

IBW male (in kg) = 50 + 2.3(Ht − 60)
IBW male (in kg) = 50 + 2.3(68 − 60)
IBW male (in kg) =68.4 kg

$$\%\ overweight\ = \frac{ABW - IBW}{IBW}.100$$

$$\%\ overweight\ = \frac{120 - 68.4}{68.4}.100$$

$$\%\ overweight\ = 105\%$$

$$CrCl\ (male) = \frac{(137 - age)[(0.285\ wt) + (12.1\text{Ht}^2\ )]}{51Scr}$$

$$CrCl\ (male) = \frac{(137 - 59)[(0.285 * 120\ ) + (12.1 * 1.7^2\ )]}{51 * 2.4}$$

$$CrCl\ (male) = 49\ mL/min$$

***Cl (in mL/min) = 1.303 (CrCl in mL/min) + 20**

Cl (in mL/min) = 1.303 (49) + 20

Cl = 84 mL/min

***V (in L) = 226 + [(298 · CrCl)/ (29.1 + CrCl)]**

V (in L) = 226 + [(298 · 49)/ (29.1 + 49)]

V = 413 L

Q7. A 62-year-old, 65-kg male with hepatic cirrhosis (total bilirubin = 2.6 mg/dL, serum albumin = 2.5 mg/dL, prothrombin time prolonged over normal by 8 seconds, slight amount of ascitic fluid, no hepatic encephalopathy) and severe chronic obstructive pulmonary disease needs to have an initial theophylline dose computed. The patient is not a tobacco smoker and does not have heart failure. Compute the patient's Child- Pugh score, estimated theophylline clearance, and theophylline dose to achieve a steady-state concentration equal to 10 mg/L.

Answer;

Age = 62 years, wt = 65 kg,

* From the following table; we calculate the child pugh scores

TABLE 3-2 Child-Pugh Scores for Patients with Liver Disease[27]

TEST/SYMPTOM	SCORE 1 POINT	SCORE 2 POINTS	SCORE 3 POINTS
Total bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged over control)	<4	4–6	>6
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Moderate	Severe

1. total bilirubin = 2.6 mg/dL → 2 points
2. serum albumin = 2.5 mg/dL →3 points
3. prothrombin time prolonged over normal by 8 seconds → 3 points
4. slight amount of ascitic fluid → 2 points
5. no hepatic encephalopathy → 1 point

Total scores = 11 points (need to change dose by 50%).

- Pt with hepatic cirrhosis and severe chronic obstructive pulmonary disease needs to have initial theophylline dose computed .
- Estimate theophylline clearance from the following table;

TABLE 3-3 Theophylline Clearance and Dosage Rates for Patients with Various Disease States and Conditions[28]

DISEASE STATE/CONDITION	MEAN CLEARANCE (mL/min/kg)	MEAN DOSE (mg/kg/h)
Children 1–9 years	1.4	0.8
Children 9–12 years or adult smokers	1.25	0.7
Adolescents 12–16 years or elderly smokers (>65 years)	0.9	0.5
Adult nonsmokers	0.7	0.4
Elderly nonsmokers (>65 years)	0.5	0.3
Decompensated CHF, cor pulmonale, cirrhosis	0.35	0.2

Mean volume of distribution = 0.5 L/kg.

Cl = 0.35mL/min/kg

Cl = 22.8 mL/min/65 kg

- Estimated theophylline dose to achieve a steady-state concentration equal to 10 mg/L.

MD = Css.Cl

MD = 10 mg/mL* (22.8* 60/1000)L/h

MD = 14 mg/h