Therapeutic Drug Monitoring

Drug Dosing in Population with Renal disease

- **Renal or hepatic disease** will decrease the elimination or metabolism of the majority drugs and change the clearance of the agent.
- **Dialysis procedures**, conducted using artificial kidneys in patients with renal failure, remove some medications from the body while the pharmacokinetics of other drugs are not changed.
- **Heart failure** results in low cardiac output which decreases blood flow to eliminating organs, and the clearance rate of drugs with moderate-to-high extraction ratios are particularly sensitive to alterations in organ blood flow.
- **Obesity** adds excessive adipose tissue to the body which may change the way drugs distribute in the body and alter the volume of distribution for the medication.
- **Drug interactions** can inhibit or induce drug metabolism, alter drug protein binding, or change blood flow to organs that eliminate or metabolize the drug.

Renal function

- Most water-soluble drugs are eliminated unchanged to some extent by the kidney.
- In addition, drug metabolites that were made more water soluble via oxidation or conjugation are typically removed by renal elimination.
- Unbound drug molecules that are relatively small are filtered at the glomerulus.
- Glomerular filtration is the primary elimination route for many medications.

Renal function

- When infants are born, renal function is not yet completely developed in full-term neonates (~40 weeks gestational age).
- However, kidney development is complete and renal function stabilizes 3–6 months after birth.
- In premature infants (<35 weeks), kidney development may take even longer during the postpartum period.
- 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 aged, 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;

- Acute injury associated with 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 the lost kidney function

Measurement of creatinine clearance

- Glomerular filtration rate can be determined by administration of special test compounds such as *inulin* or *^{125}I-iothalamate*; this is sometimes done for patients when precise determination of renal function is needed.

- Glomerular filtration rate (GFR) can be estimated using the modified Modification of Diet in Renal Disease (MDRD) equation:
  GFR (in mL/min / 1.73 m2) = 186 · SCr−1.154 · Age−0.203 · (0.742, if female) · (1.21, if African-American).
  For example, the estimated GFR for a 53-year-old African-American male with a SCr = 2.7 mg/dL would be computed as follows:
  GFR = 186·(2.7 mg/dL)−1.154 · (53 y)−0.203·1.21 = 32 mL/min / 1.73 m2
  .

However, 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). Creatinine is a by-product of muscle metabolism that is primarily eliminated by glomerular filtration. Because of this property, it is used as a surrogate measurement of glomerular filtration rate. Since creatinine is also eliminated by other routes, CrCl does not equal GFR, so the two parameters are not interchangeable.

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.

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

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 (mL/min) = (UCr · Vurine) / (SCr · T)
= (55 mg/dL · 1000 mL) /(1.0 mg/dL · 1440 min)
= 38 mL/min.

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

- This realization has prompted investigators to derive methods which estimate creatinine clearance from serum creatinine values and other patient characteristics in various populations.

- 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,

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

- For females,

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

- 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

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

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

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;

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

$$= [(140 - 55\ y)80\ kg] / (72 \cdot 1.9\ mg/dL)$$

$$= 50\ mL/min.$$

Estimation of creatinine clearance

- Some patients have decreased muscle mass due to disease states and conditions that affect muscle or prevent exercise.
- 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***
- The first step in this method is to estimate creatinine production:

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

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

Ess: excretion of creatinine
IBW: ideal body weight (kg)
Age (years)

Estimation of creatinine clearance

The remainder of the equations correct creatinine production for renal function, and adjust the estimated creatinine clearance value according to whether the renal function is getting better or worse:

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

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

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

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, other methods to estimate creatinine clearance should be used.
- It has been suggested that use of ideal body weight or adjusted body weight (ideal body weight plus 40% of obese weight) instead of actual body weight in the Cockcroft-Gault equation, gives an adequate estimate of creatinine clearance for obese individuals

Estimation of creatinine clearance

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

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

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

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,

$$\text{CrClest (in mL/min / 1.73 m2)} = (0.45 \cdot \text{Ht}) \,/\, \text{SCr}$$

age 1–20 years,

$$\text{CrClest (in mL/min / 1.73 m2)} = (0.55 \cdot \text{Ht}) / \text{SCr}$$

Ht: height (cm)

SCr: serum creatinine (mg/dL)

Estimation of drug dosing using creatinine clearance

- It is common to base initial doses of drugs that are renally eliminated on creatinine clearance.
- The basis for this is that renal clearance of the drug is smaller in patients with a reduced glomerular filtration rate.
- However, clinicians should bear in mind that the suggested doses for patients with renal impairment is an initial guideline only, and doses may need to be increased in patients that exhibit suboptimal drug response and decreased in patients with adverse effects.

Estimation of drug dosing using creatinine clearance

- Generally, one should consider a possible,
  - *modest decrease in drug doses when Clcr* $< 50-60\ mL/min$
  - *moderate decrease in drug doses when Clcr* $< 25-30$ *mL/min*
  - *substantial decrease in drug doses when Clcr* $\leq 15\ mL/min$

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

- The approach of doses modification used depends on:

  - *Route of administration*
  - *Dosage forms available*
  - *Pharmacodynamic response to the drug*

Estimation of drug dosing using creatinine clearance

- For example, if the drug is prescribed orally and only a limited number of solid dosage forms are available, one will usually administer the usual dose and increase the dosage interval.
- If the drug is given parenterally, a smaller dose can be administered, and it is more likely that the usual dosage interval will be retained.

Estimation of drug dosing using creatinine clearance

- For drugs with narrow therapeutic ranges (aminoglycoside and vancomycin) both the dose and dosage interval can be manipulated to achieve the targeted levels.
- If the drug dose is reduced and the dosage interval remains unaltered in patients with decreased renal function, maximum drug concentrations are usually lower and minimum drug concentrations higher than that in patients with normal renal function receiving the typical drug dose.
- If the dosage interval is prolonged and the drug dosage remains the same, maximum and minimum drug concentrations are usually about the same as in patients with good renal function receiving the usual drug dose.

Estimation of drug dosing using creatinine clearance

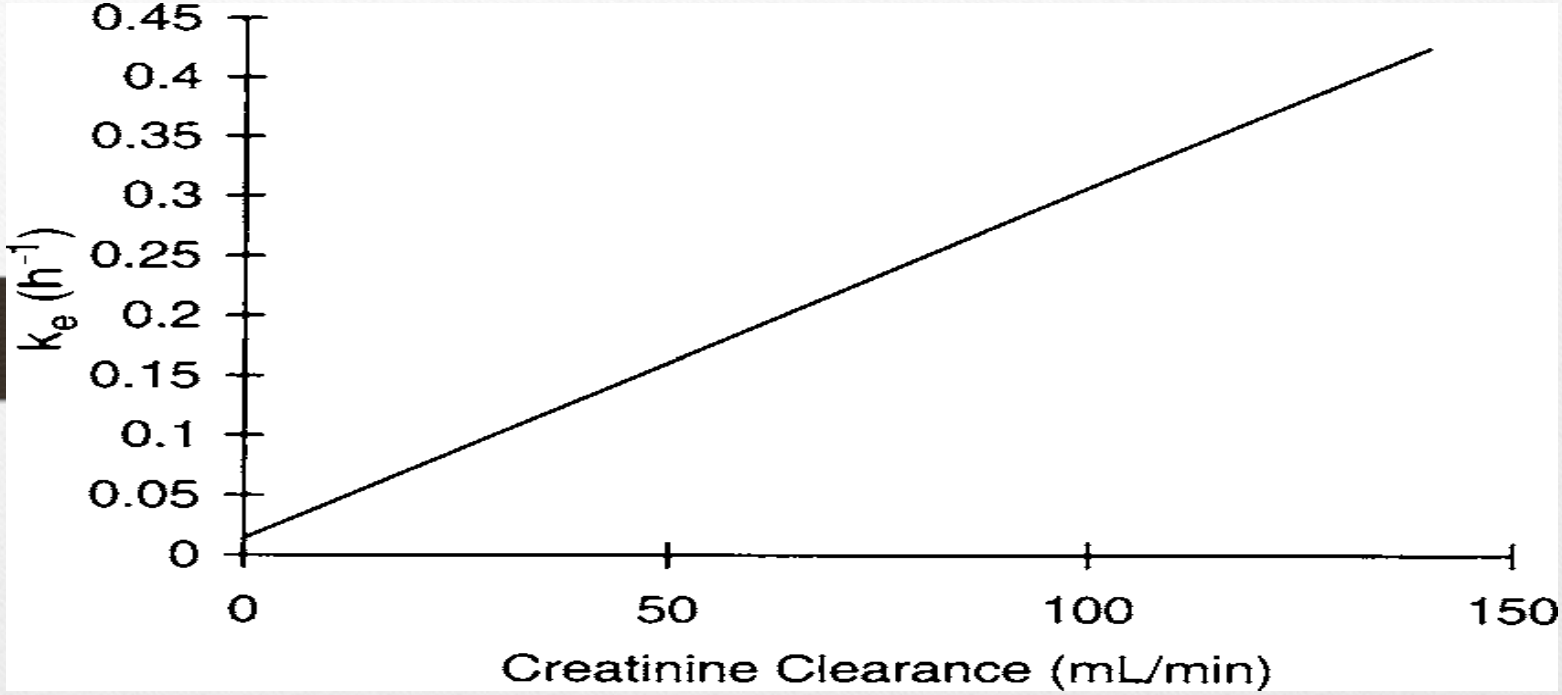
- For drugs with narrow therapeutic indexes, Clcr may be used to estimate pharmacokinetic parameters for a patient based on prior studies conducted in other patients with renal dysfunction.
- Elimination rate constant (ke) can also be estimated using Clcr, but it is a dependent pharmacokinetic parameter whose result is reliant on the relative values of clearance and volume of distribution (ke = Cl/V).
- Because of this, changes in elimination rate constant may not always be due to changes in the renal elimination of the drug.

Estimation of drug dosing using creatinine clearance

- The relationship between (ke) and Clcr is usually approximated by a straight line with a slope that is a function of renal elimination for the agent and an intercept that is related to the elimination of drug in functionally anephric patients (glomerular filtration rate ≈ 0)

- Relationship between Clcr and aminoglycoside elimination rate constant (ke) used to estimate initial aminoglycoside elimination when no drug concentrations are available. The y-axis intercept (0.014 h–1) is non-renal elimination for aminoglycosides.

Estimation of drug dosing using creatinine clearance



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

Estimation of drug dosing using creatinine clearance

The relationship between drug clearance and creatinine clearance is usually approximated by a straight line with a slope that is a function of the renal clearance for the drug and an intercept that is related to the non-renal clearance of the drug.

For digoxin,

Cl (in mL/min) = 1.303 · CrCl + ClNR

where **ClNR** is non-renal clearance and equals **20 mL/min** in patients with moderate-severe heart failure and **40mL/min** in patients with no or mild heart failure

Estimation of drug dosing using creatinine clearance

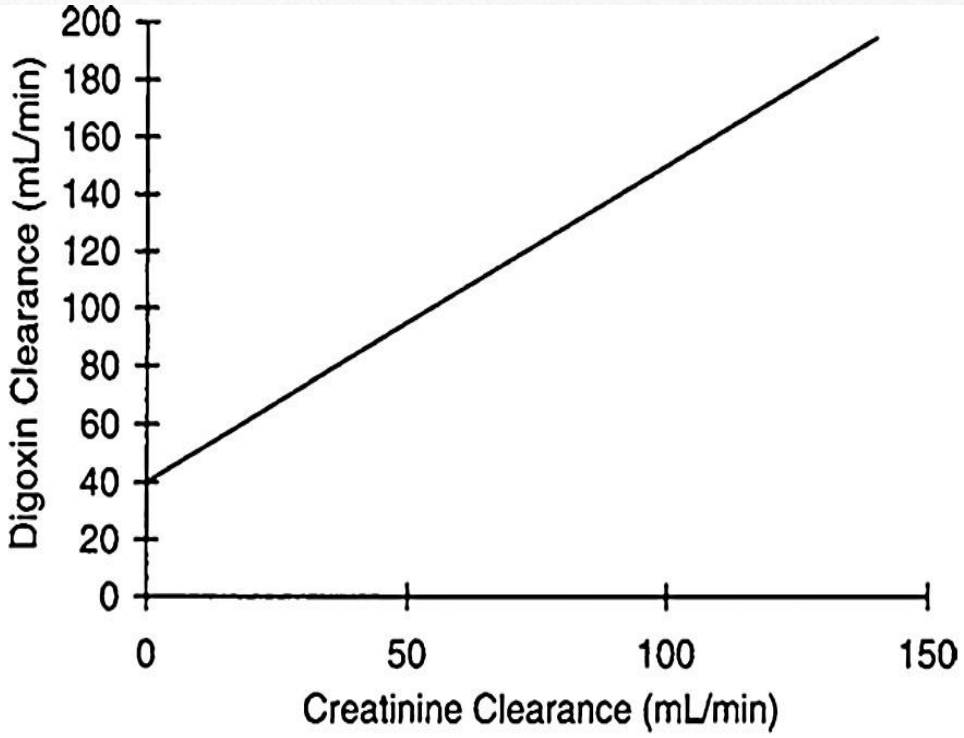


FIGURE 3-3 Relationship between creatinine clearance and digoxin clearance used to estimate initial digoxin clearance when no drug concentrations are available. The y-axis intercept (40 mL/min) is nonrenal clearance for digoxin in patients with no or mild heart failure. If the patient has moderate to severe heart failure, nonrenal clearance is set to a value of 20 mL/min.

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 that would normally be eliminated by the kidney but accumulate in the blood of patients with poor kidney function can increase the volume of distribution of other 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;

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

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