Practice problems

Q1: A patient with tonic-clonic seizures is given phenobarbital 100 mg intravenously daily until steady-state occurs. Pharmacokinetic constants for phenobarbital in the patient are: k = 0.116 d^{-1}, V_D = 75 L. Calculate the steady-state concentration 23 hours after the last dose.

Solution
The steady-state concentration following multiple IV injections can be calculated by the following equation

$$\boldsymbol{C = \frac{D}{V_D} . \left(\frac{e^{-kt}}{1 - e^{-k\tau}}\right)}$$

23 hours after the last dose = $\frac{23}{24}$ = 0.96 d

$$\boldsymbol{C = \frac{100}{75} . \left(\frac{e^{-0.116\ x\ 0.96}}{1 - e^{-0.116\ x\ 1}}\right)} = 10.9 \text{ mg/L}$$

Q2: A patient with gram-negative pneumonia is administered tobramycin 140 mg every 8 hours until steady state is achieved. Pharmacokinetic parameters for tobramycin in the patient are: V = 16 L, k = 0.30 h^{-1}. Calculate the steady-state concentration immediately after a 1-hour infusion. Note tobramycin is administered as an infusion over 1 hour.

Solution

$$C = \frac{K_0}{KV_D} \left(\frac{1-e^{-kt\prime}}{1 - e^{-k\tau}}\right)$$

$$C = \frac{140}{0.3\ x\ 16} \left(\frac{1-e^{-0.3\ x\ 1}}{1 - e^{-0.3\ x\ 8}}\right) = 8.3 \text{ mg/L}$$

Q3: A patient with an arrhythmia is administered 250 mg of quinidine orally (as 300 mg quinidine sulfate tablets) every six hours until steady state occurs. Pharmacokinetic constants for quinidine in the patient are: V = 180 L, k = 0.0693 h^{-1}, F = 0.7. Calculate the postabsorption, postdistribution steady-state concentration just before the next dose

Solution
Just before the next dose means that the time of calculating the plasma concentration is 6 hours (t = 6).

$$\boldsymbol{C = \frac{FD}{V_D} . \left(\frac{e^{-kt}}{1 - e^{-k\tau}}\right)}$$

$$\boldsymbol{C = \frac{0.7\ 300}{180} . \left(\frac{e^{-0.0693\ x\ 6}}{1 - e^{-0.0693\ x\ 6}}\right)} = 1.9 \text{ mg/L}$$

Q4: A patient receiving theophylline 300 mg intravenously every 6 hours has a predose concentration equal to 2.5 mg/L and postdose concentrations of 9.2 mg/L one hour and 4.5 mg/L five hours after the second dose is given. Calculate k and V_D.
Solution

$$K = - \frac{\log C2 - \log C1}{t2 - t1} \times 2.3$$

$$K = - \frac{\log 4.5 - \log 9.2}{5 - 1} \times 2.3 = 0.179^{-1} \text{ h.}$$

$$V_D = \frac{D}{(C_0 - C_{predose})}$$

C_0 can be calculated from following equation

$$\boldsymbol{C = C_0 . e^{-kt}}$$

$$\boldsymbol{4.5 = C_0 . e^{-0.179 \, x \, 5}}$$

$$\boldsymbol{C_0 =} \text{ 11 mg/L}$$

$$V_D = \frac{300}{11 - 2.5} = 35.3 \text{ L}$$

Q5: a patient is prescribed gentamicin 100 mg infused over 60 minutes every 12 hours. A predose steady-state concentration ($C_{predose}$) is drawn and equals 2.5 mg/L. After the 1-hour infusion, a steady-state maximum concentration (C_{max}) is obtained and equals 7.9 mg/L. Calculate k and V_D

Solution
Since the patient is at steady state, it can be assumed that all predose steady-state concentrations are equal. Because of this the predose steady-state concentration 12 hours after the dose can also be considered equal to 2.5 mg/L and used to compute the elimination rate constant (k) of gentamicin for the patient:

$$K = - \frac{\log C2 - \log C1}{t2 - t1} \times 2.3$$

$$K = - \frac{\log 2.5 - \log 7.9}{12 - 1} \times 2.3 = 0.105^{-1} \text{ h.}$$

$$V_D = \frac{k_0 \, (1 - e^{-kt\prime})}{k \, [\, C_{max} - (C_{predose} \, . \, e^{-kt\prime})}$$

$$VD = \frac{100 \, mg/1h \, (1 - e^{-0.105 \, x \, 1})}{0.105 \, [\, 7.9 - (2.5 \, . \, e^{-0.105 \, x \, 1})} = 16.8 \text{ L}$$

Q6: A patient is given procainamide capsules 750 mg every 6 hours. The following concentrations are obtained before and after the second dose: $C_{predose}$ = 1.1 mg/L, concentrations 2 hours and 6 hours postdose equal 4.6 mg/L and 2.9 mg/L. Calculate K and V_D.

The two concentration time points (postdose) can be used to calculate the K as follow

$$K = - \frac{\log C2 - \log C1}{t2 - t1} \times 2.3$$

$$K = - \frac{\log 2.9 - \log 4.6}{6-2} \times 2.3 = 0.115\ h^{-1}.$$

Procainamide was administered orally. However, the bioavailability is unknown. Therefore, the absolute value of V_D can't be calculated. Instead, the hybrid constant of V_D/F can be calculated as follow:

$$\frac{VD}{F} = \frac{D}{(C_0 - C_{predose})}$$

C_0 can be calculated from following equation

$$\boldsymbol{C = C_0 . e^{-kt}}$$

$$\boldsymbol{4.6 = C_0 . e^{-0.115\ x\ 2}}$$

$$\boldsymbol{C_0} = 5.8 \text{ mg/L}$$

$$\frac{VD}{F} = \frac{300}{5.8 - 1.1} = 160 \text{ L}$$

Q7: A patient is administered 250 µg of digoxin tablets daily for heart failure until steady state. The pharmacokinetic constants for digoxin in the patient are: F = 0.7, Cl = 120 L/d. Calculate he average steady-state concentration.

$$C_{ss} = \frac{[F(\frac{D}{\tau})]}{Cl}$$

$$C_{ss} = \frac{[0.7(\frac{250}{1})]}{120} = 1.5 \text{ µg/L}$$

Q8: patient is given 1500 mg of procainamide sustained release tablets every 12 hours until steady state for the treatment of an arrhythmia. The pharmacokinetic parameters for procainamide in the patient are: F = 0.85, Cl = 30 L/h. Calculate the average steady-state concentration.

$$C_{ss} = \frac{[F(\frac{D}{\tau})]}{Cl}, \qquad C_{ss} = \frac{[0.85(\frac{1500}{12})]}{30} = 3.5 \text{ mg/L}$$

Q9: Calculate the dose and the dosage interval for a patient that needs to be treated for complex partial seizures with intravenous phenobarbital. The target Css_{max} and Css_{min} are 30 and 25 mg/L, respectively. The population PK parameters for phenobarbital are: k = 0.139 d^{-1} and V_D = 50 L.

Solution

$\boldsymbol{\tau} = \frac{ln\ Css_{max} - ln\ Css_{min}}{k} = \frac{ln\ 30 - ln\ 25}{0.139}$ = 1.3 day (this value is rounded to 1 day for practical use)

D = $Css_{max}\ V_D\ (1 - e^{-k\boldsymbol{\tau}})$

D = 30 x 50 (1 - $e^{-0.139\ x\ \mathbf{1}}$) = 202 mg (this dose is rounded to 200 mg for practical use).

Therefore, the calculated dose of phenobarbital would be IV injection of 200 mg every day.

Q10: A patient receiving tobramycin for the treatment of intraabdominal sepsis. Using pharmacokinetic parameters (V_D = 20 L, k = 0.087 h^{-1}) calculate a tobramycin dose (infused over 1 hour) that would provide maximum (Css_{max}) and minimum (Css_{min}) steady-state concentrations of 6 mg/L and 1 mg/L, respectively.

$\boldsymbol{\tau} = \frac{ln\ Css_{max} - ln\ Css_{min}}{k}$ + t' , $\quad \boldsymbol{\tau} = \frac{ln\ 6 - ln\ 1}{0.087}$ + 1 = 22 h (round to practical dosage interval of 24 h)

$K_0 = Css_{max}\ k\ V_D\ (\frac{1 - e^{-k\boldsymbol{\tau}}}{1 - e^{-kt'}})$, $\quad K_0 = 6 \times 0.087 \times 20\ (\frac{1 - e^{-0.087\ x\ 24}}{1 - e^{-0.087\ x\ 1}})$ = 110 mg

The patient would be prescribed tobramycin 110 mg infused over 1 hour every 24 hours

Q11: a patient with simple partial seizures that needs to receive valproic acid capsules (population pharmacokinetic parameters are V = 12 L, k = 0.05 h^{-1}, T_{max} = 3 h, F = 1.0). Calculate the optimum dose and dosage interval to achieve maintain steady-state maximum (Css_{max}) and minimum (Css_{min}) concentrations of 80 mg/L and 50 mg/L, respectively.

$\boldsymbol{\tau} = \frac{ln\ Css_{max} - ln\ Css_{min}}{k} + T_{max}$, $\quad \boldsymbol{\tau} = \frac{ln\ 80 - ln\ 50}{0.05}$ + 3 = 12.4 h (round to a practical interval of 12 h)

D = $\frac{Css_{max}\ V_D}{F}\ (\frac{1 - e^{-k\boldsymbol{\tau}}}{e^{-k\boldsymbol{Tmax}}})$, $\quad D = \frac{80 \times 12}{1}\ (\frac{1 - e^{-0.05\ x\ 12}}{e^{-0.05\ x\ \mathbf{3}}})$ = 503 mg (round to practical dose of 500 mg)

The patient would be prescribed valproic acid capsules 500 mg orally every 12 hours.

Q12: a patient with an atrial arrhythmia needing treatment with procainamide sustained-release tablets (clearance equals 24 L/h; F = 0.85, $\boldsymbol{\tau}$ = 12 h for sustained-release tablet). The target average steady-state procainamide concentration is 5 mg/L. Calculate the dose of procainamide required to achieve this concentration.

D = $\frac{Css\ Cl\boldsymbol{\tau}}{F} = \frac{5\ x\ 24\ x\ \mathbf{12}}{0.85} = 1694\ mg$ (round to a practical dose of 1500 mg)

The patient would be prescribed procainamide sustained-release tablets 1500 mg orally every 12 hours.

Practice Problems

1. PZ is a 35-year-old, 60-kg female with a *Staphylococcus aureus* wound infection. While receiving vancomycin 1 g every 12 hours (infused over one hour), the steadystate peak concentration (obtained one-half hour after the end of infusion) was 35 mg/L, and the steady-state trough concentration (obtained immediately predose) was 15 mg/L. (A) Using one compartment IV bolus equations, compute the pharmacokinetic parameters for this patient. (B) Using the patient-specific pharmacokinetic parameters calculated in part A, compute a new vancomycin dose that would achieve Cssmax = 30 mg/L and Cssmin = 7.5 mg/L.

2. KL is a 65-year-old, 60-kg female being treated for septic shock. Among other antibiotics, she is being treated with tobramycin 60 mg every 8 hours (infused over 1 hour). Steady-state serum concentrations are: Css_{max} = 7.1 mg/L, Css_{min} = 3.1 mg/L.
   Using one compartment intermittent intravenous infusion equations, compute the pharmacokinetic parameters for this patient and use them to individualize the tobramycin dose to achieve Css_{max} = 8 mg/L and Css_{min} = 1.0 mg/L.

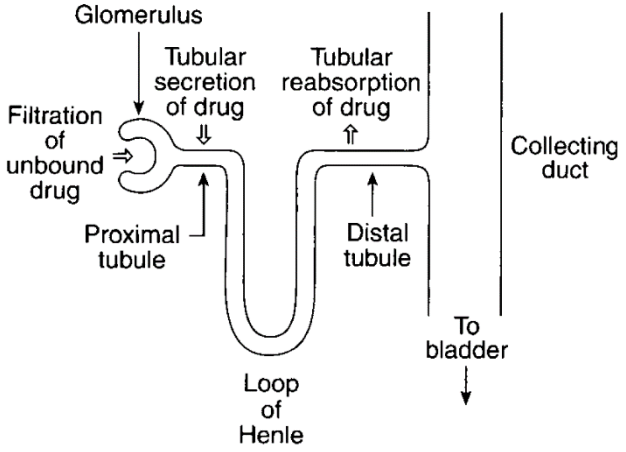
3. MM is a 54-year-old, 68-kg male being treated with procainamide 750-mg regular release capsules every 6 hours for an arrhythmia. The following steady-state concentration is available: Css_{min} = 1.5 mg/L (obtained immediately predose). Calculate a dose that will achieve a Css_{min} = 2.5 mg/L.

Drug Dosing in Special Populations

Drug Dosing in Renal Disease

The kidney is the main organ responsible for drug excretion. Three processes of drug movement occur in the kidney:

- Glomerular filtration
- Active tubular secretion
- Tubular reabsorption



The equation that describes these various routes of renal elimination is:

$$Cl_R = [\ (f_B \,.\, GFR) + \frac{RBF\,.\,(f_B\,.\,Cl'_{sec})}{RBF + (f_B\,.\,Cl'_{sec})}\ ]\ (1 - FR)$$

where f_B is the free fraction of drug in the blood, GFR is glomerular filtration rate, RBF is renal blood flow, Cl'_{sec} is the intrinsic clearance for tubular secretion of unbound drug, and FR is the fraction reabsorbed.

Measurement and Estimation of Creatinine Clearance

The measurement and estimation of creatinine clearance (CrCl) is recommended by the Food and Drug Administration (FDA) and others to estimate renal function for the purposes of drug dosing as creatinine is a by-product of muscle metabolism that is primarily eliminated by glomerular filtration.

One of the commonly used equations for the estimation of CrCl is Cockcroft-Gault method which is based on serum creatinine:

$$CrCl_{est} = \frac{[(140-age).BW]}{72\,.\,S_{Cr}} \quad \text{.....} \quad \text{for males}$$

$$CrCl_{est} = \frac{[0.85\,.\,(140-age).BW]}{72\,.\,S_{Cr}} \quad \text{.....} \quad \text{for females}$$

Where $CrCl_{est}$ is estimated creatinine clearance in mL/min, age is in years, BW is body weight in kg, and S_{Cr} is serum creatinine in mg/dL.

The Cockcroft-Gault method should only be used in

1. Patients ≥18 years old.
2. When actual weight within 30% of their ideal body weight (IBW)

   IBW_{male} (in Kg) = 50 + 2.3 (Ht – 60)
   IBW_{female} (in Kg) = 45 + 2.3 (Ht – 60)

   Where Ht is the height in inches (1 inch = 2.45 cm)
3. Stable serum creatinine concentrations.

For example, a 55-year-old, 80-kg, 5-ft 11-in male has a serum creatinine equal to 1.9 mg/dL. The estimated creatinine clearance would be

IBW_{male} (in Kg) = 50 + 2.3 (Ht – 60)

Note that 1 foot = 12 inches

IBW_{male} (in Kg) = 50 + 2.3 (71 – 60) = 75.3 kg

Therefore, BW (80 kg) is within 30% of IBW (75.3 kg) so that Cockcroft-Gault method can be used to calculate $CrCl_{est}$

$$CrCl_{est} = \frac{[(140-\text{age})/\text{BW}]}{72 \,.\, S_{Cr}} = \frac{[(140-55)/80]}{72 \,.\, 1.9} = 50 \text{ mL/min}$$

Note: in obese patients where Cockcroft-Gault method can't be used alternative equations can be applied:

$$CrCl_{est} = \frac{(137-age)[(0.285 \,.\, Wt)+(12.1 \,.\, Ht^2)]}{51 \,.\, S_{Cr}} \quad \text{..... for males}$$

$$CrCl_{est} = \frac{(146-age)[(0.287 \,.\, Wt)+(9.74 \,.\, Ht^2)]}{60 \,.\, S_{Cr}} \quad \text{..... for females}$$

Therapeutic Drug Monitoring

Lecture 4
Dr Atheer Zgair

Estimation of Drug Dosing and Pharmacokinetic Parameters Using Creatinine Clearance

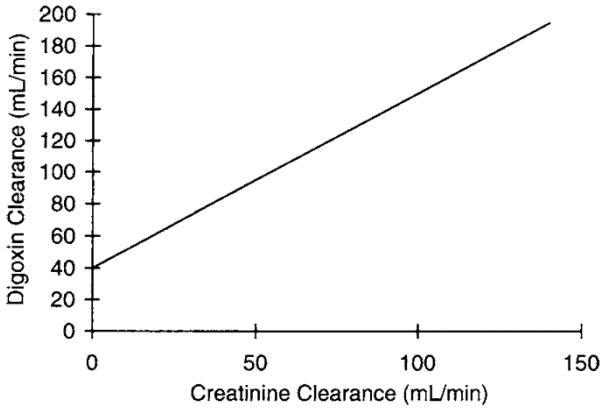
It is widely accepted that dosage adjustment is required when patient is treated with a medication that eliminated by the kidney. One of three methods is commonly used for dose adjust. These are:

1. Decrease the drug dose and retain the usual dosage interval.
2. Retain the usual dose and increase the dosage interval.
3. Simultaneously decrease the dosage and prolong the dosage interval.

For drugs with narrow therapeutic indexes, measured or estimated creatinine clearance may be used to estimate pharmacokinetic parameters for a patient based on prior studies conducted in other patients with renal dysfunction.
For example, for digoxin, an equation that describes the relationship between digoxin clearance (Cl) and creatinine clearance (CrCl in mL/min) is:

$Cl\ (in\ mL/min) = 1.303 \cdot CrCl + Cl_{NR}$

where Cl_{NR} is nonrenal clearance and equals 20 mL/min in patients with moderate-severe heart failure and 40 mL/min in patients with no or mild heart failure. This equation is derived from the linear relationship between digoxin Cl and CrCl



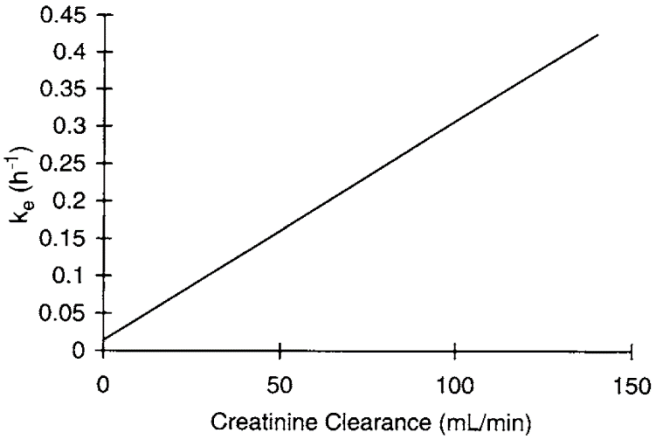
Digoxin volume of distribution decreases in patients with decreased renal function according to the following equation:

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

where CrCl is in mL/min. The decline in volume of distribution presumably occurs because of displacement of tissue-bound digoxin.

For the aminoglycoside antibiotics, an equation that represents the relationship between aminoglycoside antibiotic elimination rate constant (k) and creatinine clearance (CrCl in mL/min) is:

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



Hepatic Disease

The equation that describes hepatic drug metabolism is

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF + (f_B \cdot Cl'_{int})}$$

Where LBF is liver blood flow, f_B is the fraction of unbound drug in the blood, and Cl'_{int} is intrinsic clearance.

- Hepatic metabolism of drugs is not completely developed in neonates (~40-weeks gestational age) and continues to increase so that by age 3–6 months it is stable. In premature infants (<35 weeks), hepatic metabolism may take even longer to develop in the postpartum period.

- On a per kilogram basis, drug metabolism is more rapid in children until puberty and then metabolic rate gradually decreases to adult values.

- Elderly individuals have decreased liver mass, and it appears that hepatocytes which are still present have decreased ability to metabolize drugs.

There are two major types of liver disease: hepatitis and cirrhosis. These diseases cause the following:

1. Decrease the number of functional hepatocytes and therefore decrease hepatic clearance.
2. Liver blood flow decreases in patients with cirrhosis results in less drug delivery to still-functioning hepatocytes and depresses hepatic drug clearance even further.
3. In patients with cirrhosis, the production of biding proteins (albumin and a1-acid glycoprotein) decline which causes the free fraction of drugs in the blood increases because of a lack of binding proteins.
4. 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 causing an increase in V_D.

As a result of decreased clearance and increased V_D in hepatic disease the K is increased.
$K = Cl/V_D$

Child-Pugh Scores

The Child-Pugh score for a patient is used to estimate the ability of the liver to metabolize drug as described in the following table.

Child-Pugh Scores for Patients with Liver Disease

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

- The Child-Pugh score for a patient with normal liver function is 5.
- A Child-Pugh score equal to 8–9 is grounds for a moderate decrease (~ 25%) in initial daily drug dose for agents that are primarily (≥60%) hepatically metabolized.
- A score of 10 or greater indicates that a significant decrease in initial daily dose (~ 50%) is required for drugs that are mostly liver metabolized.

For example, the usual dose of a medication that is 95% liver metabolized is 500 mg every 6 hours, and the total daily dose is 2000 mg/d. For a hepatic cirrhosis patient with a Child-Pugh score of 12, an appropriate initial dose would be 50% of the usual dose or 1000 mg/d. The drug could be prescribed to the patient as 250 mg every 6 hours or 500 mg every 12 hours.

The method used to reduce the dose for patients with liver dysfunction will depend on the route of administration and the available dosage forms. For example, if the medication is only available as an oral capsule, it is likely that the usual dose will be given to a patient with liver disease but the dosage interval will be prolonged. However, if the drug is given parenterally, it may be possible to simultaneously modify the dose and dosage interval to attain the same maximum and minimum steady-state concentrations in patients with hepatic dysfunction as those encountered in patients with normal liver function.