DOSAGE ADJUSTMENT

Renal and Hepatic Diseases
MEASURING RENAL FUNCTION

A. Glomerular filtration rate (GFR)

1. determined from excretion rate of a freely filtered substance* (e.g., inulin) and its concentration in plasma:

\[ GFR = \frac{(Cur) \times (Qur)}{Cp} \]

where Cur is concentration in urine, Qur is urine flow rate, and Cp is concentration in plasma.

* must be a substance not actively secreted or reabsorbed.
Renal Function Overview: The Nephron

- **F** = Filtration: blood to lumen
- **R** = Reabsorption: lumen to blood
- **S** = Secretion: blood to lumen
- **E** = Excretion: lumen to external environment

Diagram shows the nephron with key parts labeled:
- Glomerulus
- Bowman's capsule
- Afferent arteriole
- Efferent arteriole
- Peritubular capillaries
- Proximal tubule
- Distal tubule
- Loop of Henle
- Collecting duct
- To renal vein
- To bladder and external environment
2. we usually use creatinine clearance (Clcr) as an index of GFR
   a. creatinine is an easily measured endogenous substance
   b. creatinine rises in proportion to decreases in GFR
Fig. 16–4. The mean plasma concentration-time profiles of cefepime, a cephalosporin antibiotic, are different in patients with varying degrees of renal function after i.v. infusion of a 1000-mg dose over 30-min. The subjects were grouped according to their measured creatinine clearance values (in mL/min). (Adapted from Barbhaiya, R.H., Knupp, C.A., Fargue, S.T., Matzke, G.R., Guay, D.R.P., and Pittman, F.A.: Pharmacokinetics of cefepime in subjects with renal insufficiency. Clin. Pharmacol. Ther., 48:268–276, 1990.)

Fig. 16–5. Sketch of the amount of amikacin sulfate in the body with time following a regimen of 500 mg every 12 hr in a patient whose renal function is normal, curve A, and in a patient whose age and weight are the same but whose renal function is 17% of normal, colored curve B. Intravenous bolus administration is simulated. The normal half-life is assumed to be 2 hr. The dashed lines are the average plateau values.
where age and weight are in years and kilograms, respectively. Now, under any condition,

\[ Clu(d) = Clu_R(d) + Clu_{NR}(d) \]

**Fig. 16-6.** The total clearance of the cephalosporin, ceftazidime, varies linearly with creatinine clearance in a group of 19 patients with varying degrees of renal function. Note that some clearance remains (y-intercept) when there is no renal function. (Drawn from the data of van Dalen, R., Vree, T.B., Baars, A.M., and Termond, E.: Dosage adjustment for ceftazidime in patients with impaired renal function. Europ. J. Clin. Pharmacol., 30:597–605, 1986.)
c. Assumptions* of using Clcr as an accurate estimate of GFR:

1.) daily anabolic production of creatine by the liver is constant
2.) daily anabolic conversion of creatine to creatinine in striated muscle is constant
3.) creatinine is only removed from the serum by filtration
4.) measurement is accurate
5.) urine collection is complete

* all of these assumptions are invalid at least part of the time
d. normal creatinine clearance values
healthy young male:
125 ml/min/1.73m²
healthy young female:
115 ml/min/1.73m²
by 60 years of age, reduced to about 70% of young adult
Several investigators have developed mathematical relationships to estimate CLcr when urine is unavailable. These factors include age, gender, weight, and serum creatinine concentration.

Perhaps the most widely used of these estimators is the one developed by Cockcroft and Gault, which identified age and body mass as factors that significantly improved the estimate of CLcr.
### TABLE 41-4. Sensitivity and Clinical Utility of Renal Function Tests

<table>
<thead>
<tr>
<th></th>
<th>Accuracy</th>
<th>Clinical Utility</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inulin clearance</td>
<td>+++</td>
<td>+</td>
<td>$$$</td>
</tr>
<tr>
<td>Radiolabeled markers</td>
<td>+++</td>
<td>+</td>
<td>$$</td>
</tr>
<tr>
<td>Nonisotopic contrast agents</td>
<td>+++</td>
<td>++</td>
<td>$$</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>++</td>
<td>+++</td>
<td>$</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>+</td>
<td>+++</td>
<td>$</td>
</tr>
</tbody>
</table>

+, least acceptable; ++, adequate; +++, better; ++++, best.
Estimation of Creatinine Clearance

Cockcroft and Gault

\[
CL_{CR} (ml / min)[\text{male}] = \frac{(140 - Age) \times IBW}{72 \times SrCr_{ss}}
\]

\[
CL_{CR} (ml / min)[\text{female}] = \frac{(140 - Age) \times IBW}{85 \times SrCr_{ss}}
\]

\[
CL_{CR} (ml / min)[\text{female}] = 0.85 \times CL_{CR\text{male}}
\]

Age: years, Weight: Kg, SrCr: mg/dl
The Cockcroft-Gault method should only be used in patients
1) ≥18 years old,
2) actual weight within (20-30)% of their ideal body weight (IBW) and
3) stable serum creatinine concentrations.

\[
\begin{align*}
\text{IBW (males)} &= 50 + 0.9 \times (\text{height} > 150 \text{cm}) \\
\text{IBW (females)} &= 45 + 0.9 \times (\text{height} > 150 \text{cm}) \\
\text{Adjusted Body Weight (AdjBW)} &= \text{IBW} + 0.4(\text{TBW} - \text{IBW})^{12}
\end{align*}
\]
Example

A 55-year-old, 80-kg, 178 cm male has a serum creatinine equal to 1.9 mg/dL. The estimated creatinine clearance would be:
INFLUENCE OF RENAL DISEASE ON KINETIC PARAMETERS

A. Absorption

Data are somewhat contradictory and therefore inconclusive.

2. Difficult to detect a change, as alterations in other variables such as protein binding, apparent volume of distribution, metabolism, and/or renal clearance could all mask impact of renal disease on oral absorption.
Apparent Volume of Distribution at Steady-State (Vdss)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Normal</th>
<th>ESRD*</th>
<th>%Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>0.20</td>
<td>0.29</td>
<td>45</td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>0.14</td>
<td>0.26</td>
<td>86</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>2.60</td>
<td>4.90</td>
<td>89</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>0.64</td>
<td>1.40</td>
<td>119</td>
</tr>
<tr>
<td><strong>Increased</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Decreased</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>0.87</td>
<td>0.60</td>
<td>31</td>
</tr>
<tr>
<td>Digoxin</td>
<td>7.30</td>
<td>4.10</td>
<td>44</td>
</tr>
<tr>
<td>Pindolol</td>
<td>2.10</td>
<td>1.10</td>
<td>48</td>
</tr>
</tbody>
</table>

* ESRD = end stage renal disease; Adapted from Table 8-6; Applied Pharmacokinetics, 3rd Edition
DOSING IN RENAL IMPAIRMENT/FAILURE

A. Most methods depend upon:
   1. accurate estimate of renal function
   2. knowledge of fraction of drug renally eliminated
   3. assumption of 1st order kinetics

Goal of dosage adjustment
1. attainment of certain peak and/or trough concentration,
2. attainment of certain steady-state concentration, or
3. attainment of certain AUC
In general
1. loading doses do not need to be changed unless Vd is changed with renal dysfunction (e.g., digoxin Vd reduced as much as 25-50% in renal failure)

2. maintenance doses (can change dose or interval)
   a. changing the interval causes greater fluctuations in concentrations but is less costly
   b. changing the doses is more costly but is associated with less fluctuation in concentrations
When to adjust

1) More Than 30 % of the drug is excreted in urine

AND

1) The decrease in renal function is more than 30 %
### TABLE 3-1 Manufacturer’s Recommended Dosing Schedule for Renal Dysfunction and Hemodialysis Patients Receiving Gabapentin

<table>
<thead>
<tr>
<th>CRCL (mL/min)</th>
<th>DAILY DOSE (mg/d)</th>
<th>DOSAGE (mg)</th>
<th>DOSAGE (mg)</th>
<th>DOSAGE (mg)</th>
<th>DOSAGE (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>900–3600</td>
<td>300 TID</td>
<td>400 TID</td>
<td>600 TID</td>
<td>800 TID</td>
</tr>
<tr>
<td>30–59</td>
<td>400–1400</td>
<td>200 BID</td>
<td>300 BID</td>
<td>400 BID</td>
<td>500 BID</td>
</tr>
<tr>
<td>15–29</td>
<td>200–700</td>
<td>200 QD</td>
<td>300 QD</td>
<td>400 QD</td>
<td>500 QD</td>
</tr>
<tr>
<td>15*</td>
<td>100–300</td>
<td>100 QD</td>
<td>125 QD</td>
<td>150 QD</td>
<td>200 QD</td>
</tr>
</tbody>
</table>

**Supplemental post-hemodialysis dose (mg)**

| Hemodialysis  | 125** | 150** | 200** | 250** | 350** |

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Case 1
Lincomycin is given in a dose of 600 mg every 6 hours to a 75-kg normal patient.
What doses would be used (Renal clearance for licomycin = 60 % and the normal half-life is 4.6 hours)
1) In complete renal shutdown?
2) When Clcr is 10 ml/min?
Case 2
The maintenance dose of gentamicin is 80 mg every 6 hours for a patient with normal renal function. Calculate the maintenance dose for a uremic patient with creatinine clearance of 20 ml/min?
Case 3
Using the method of Cockroft and Gault, calculate the creatinine clearance for a woman (38 years old, 62 kg) whose serum creatinine is 1.8 mg/dl. (Answer is 41.5ml/min)

Case 4
Would you adjust the dose of cephamandole, an antibiotic which is 98% excreted unchanged in urine, for the patient in case 3? Why?
Case Study:
Calculate an appropriate dosing regimen for the following male patient (Xo, $\tau$, XL); age = 56 years, weight = 62kg. Normally this drug has a half-life of 3 hours and 70% excreted in urine. Apparent volume of distribution is calculated as $0.28\text{L/Kg}$. Develop a dosing regimen to keep the peak concentration close to but below $6 \mu g/ml$ and the trough concentration below but close to $1.0 \mu g/ml$

1) Clcr is normal
2) Clcr is 40 % of normal.
A patient is using three drugs, A, B and C. Drug A is 100% eliminated by the kidneys. Drug B is 70% eliminated by the kidneys. Drug C is entirely eliminated via hepatic metabolism.

The patient has suffered from acute renal failure leading to Reduction in the creatinine clearance by 40% provided that the elimination half-lives for the three drugs are 6, 9 and 4 hours for drug A, B and C respectively.

Find out the followings:
1) Changes in the elimination half-lives of the three drug.
2) The new maintenance doses that will produce the same average plasma concentration produced by the original doses, previous maintenance doses are:
   - for drug A 10 mg/day
   - for drug B 30 mg/day
   - for drug C 50 mg/day
Case
1) A 60 yr, 72 kg male admitted to the hospital because of severe pneumonia. His serum creatinine was 2.0 mg/dl. Estimate the creatinine clearance for this patient.
30 ml/min
40 ml/min
120 ml/min
60 ml/min
The average renal clearance of tetracycline is 3.5 L/hr, while its average total body clearance is 7 L/hr. What is the fraction of tetracycline bioavailable dose excreted unchanged in urine?

0.10  
0.25  
0.50  
0.80
Tetracycline is a broad spectrum antibiotic that is used to treat a variety of infections. If the average dose of tetracycline in adult patients with normal kidney function is 500 mg every 8 hours, what will be the dose required in a patient with only 20% of the normal kidney function if 50% of tetracycline dose is excreted unchanged in urine?

- 250 mg q 8 hr
- 300 mg q 8 hr
- 500 mg q 8 hr
- 200 mg q 8 hr
Ranitidine is an H2-receptor antagonist used in the treatment of peptic ulcer. After administration of the average dose of ranitidine in patients with normal kidney function (150 mg q 12 hr), 70% of the dose is excreted unchanged in urine. What will be the ranitidine dose required in a patient with only 30% of normal kidney function?

- 30 mg q 12 hr
- 45 mg q 12 hr
- 100 mg q 12 hr
- 75 mg q 12 hr
Dosage Regimen Design and Adjustment for Aminoglycosides
<table>
<thead>
<tr>
<th>Drug</th>
<th>Peak Concentration</th>
<th>Trough Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin</td>
<td>Conventional</td>
<td>Once-daily Dosing</td>
</tr>
<tr>
<td></td>
<td>5-8 mg/L</td>
<td>20 mg/L</td>
</tr>
<tr>
<td></td>
<td>&lt; 2 mg/L</td>
<td>Undetect.</td>
</tr>
<tr>
<td>Tobramicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>Peak</td>
<td>20-30 mg/L</td>
</tr>
<tr>
<td></td>
<td>20-30 mg/L</td>
<td>60 mg/L</td>
</tr>
<tr>
<td></td>
<td>&lt; 10 mg/L</td>
<td>Undetect.</td>
</tr>
</tbody>
</table>
VOLUME OF DISTRIBUTION (V)

The volume of distribution of the aminoglycosides is \(=0.25 \text{ L/kg}\) [wide range of 0.1 to 0.5 L/kg has been reported].

Since aminoglycosides distribute very poorly into adipose tissue, lean rather than total body weight (TBW) should result in a more accurate approximation of \(V\) in obese patients.
The aminoglycoside volume of distribution in obese subjects also could be adjusted based on the patient's ideal body weight (IBW) plus 10% of his or her excess weight.

[aminoglycoside antibiotics appear to distribute into extracellular space, which is approximately 10% of total body weight]

\[ Vd(L) = (0.25 \times IBW) + 0.1 \times (TBW - IBW) \]
CLEARANCE (CI)

The aminoglycoside antibiotics are eliminated almost entirely by the renal route.

Since the aminoglycoside and creatinine clearances are similar over a wide range of renal function, aminoglycoside clearance can be estimated from the formulas used to estimate creatinine clearance when concentrations are within the therapeutic range.
ELIMINATIONHALF-LIFE

The elimination half-life of aminoglycoside antibiotics from the body is a function of the volume of distribution and clearance. Since renal function varies considerably among individuals, the half-life is also variable.

For example, a 70-kg, 25-year-old man with a serum creatinine of 0.8 mg/dL might have an aminoglycoside clearance of 100 mL/min or more. If his volume of distribution is 0.25 L/kg, the corresponding elimination half-life will be approximately 2 hours.

In contrast, a 75-year-old man with a similar V and a serum creatinine of 1.4 mg/dL might have an aminoglycoside clearance of ≈35 mL/min and a half-life of approximately 6 hours.
Liver characteristics

1. receives “dual” blood supply
   a. 25-35% hepatic artery
   b. 65-75% portal vein
   c. 1.5 L/min in normal adults
The liver plays a central role in the absorption and disposition kinetics of most drugs. It is not only the most important biotransformation site, but parameters such as liver blood flow, binding to plasma proteins and biliary excretion, which can all potentially influence drug pharmacokinetics, depend upon the normal functioning of this organ.
Absorption

The effect of chronic liver disease on the bioavailability of orally administered drugs is mainly the result of reduced presystemic hepatic metabolism.

As a consequence of the unique position of the liver in the circulatory system, all drugs absorbed from the gastrointestinal tract (with exception of the mouth and the lower part of the rectum) are exposed to the metabolizing enzymes and biliary excretion mechanisms of the liver.
### Table 2  Oral bioavailability of certain flow-limited drugs in patients with cirrhosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral bioavailability</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>Cirrhotics</td>
</tr>
<tr>
<td>clomethiazole</td>
<td>0.10 ± 0.07</td>
<td>1.16 ± 0.25</td>
</tr>
<tr>
<td>encainide</td>
<td>0.26 ± 0.20</td>
<td>0.76 ± 0.42</td>
</tr>
<tr>
<td>flumazenil</td>
<td>0.28 ± 0.06</td>
<td>0.65 ± 0.26</td>
</tr>
<tr>
<td>labetalol</td>
<td>0.33 ± 0.09</td>
<td>0.63 ± 0.19</td>
</tr>
<tr>
<td>meperidine</td>
<td>0.48 ± 0.13</td>
<td>0.87 ± 0.27</td>
</tr>
<tr>
<td>midazolam</td>
<td>0.38 ± 0.16</td>
<td>0.76 ± 0.37</td>
</tr>
<tr>
<td>morphine</td>
<td>0.47 ± 0.14</td>
<td>1.01 ± 0.43</td>
</tr>
<tr>
<td>nifedipine</td>
<td>0.51 ± 0.17</td>
<td>0.91 ± 0.26</td>
</tr>
<tr>
<td>nisoldipine</td>
<td>0.04 ± 0.02</td>
<td>0.15 ± 0.10</td>
</tr>
<tr>
<td>pentazocine</td>
<td>0.18 ± 0.05</td>
<td>0.68 ± 0.21</td>
</tr>
<tr>
<td>propranolol</td>
<td>0.36 ± 0.02</td>
<td>0.60 ± 0.10</td>
</tr>
<tr>
<td>verapamil</td>
<td>0.10 ± 0.02</td>
<td>0.16 ± 0.05</td>
</tr>
</tbody>
</table>
Distribution

Since only the unbound drug is capable of entering and leaving the tissue compartments, the distribution of a drug within the body depends on the reversible binding of drugs to blood cells, plasma proteins and tissue macromolecules.

Many drugs, which are highly bound to albumin or $\alpha_1$-acid glycoprotein, have a significantly higher fu in patients with chronic liver disease.
Mechanisms for decreased binding of certain drugs to plasma proteins include (1) reduced albumin and $\alpha_1$-acid glycoprotein synthesis leading to low levels of these important binding proteins in plasma of patients with chronic liver disease, and (2) accumulation of endogenous compounds, such as bilirubin, inhibiting plasma protein binding of drugs.
As a result of the lower plasma binding, the distribution volume of certain drugs may be larger in these patients.

Moreover, water soluble drugs will have a significant increase in their volumes of distribution in patients with ascites possibly necessitating larger loading doses.
In addition, fu is also an important determinant of the systemic and oral clearance of capacity-limited drugs. To correctly interpret the effect of liver disease on the plasma or blood clearance of capacity-limited drugs exhibiting high plasma protein binding, one should take alterations in fu into account. Failing to do so has led on many occasions to misinterpretations of the experimental data.
PHARMACOKINETIC PRINCIPLES

A. Hepatic Extraction Ratio (ER)
1. removal from systemic circulation on each “pass” through liver, or removal from splanchnic blood via “first pass”
2. ER describes efficiency of drug removal
   \[
   ER = \frac{(Ca - Cv)}{Ca}
   \]
   where \( Ca = \) drug concentration in blood going into the liver and
   \( Cv = \) drug concentration in blood leaving the liver
   a. ER can vary from 0 to 1
   b. a measure of the liver’s effectiveness in extracting drug from the blood as it perfuses the hepatic sinusoids
Bioavailability (F)

1. F is the amount of an orally administered drug that reaches the systemic circulation (assuming 100% absorption)

\[ F = 1 - ER \text{ or } \frac{Div \times AUCo}{Do \times AUCiv} \]

2. Hepatic disease or drug-induced changes in first pass effect can significantly alter F for a drug that is efficiently extracted
Hepatic Intrinsic Clearance (CLuint)
Definition: the maximum ability of the hepatocytes to irreversibly remove unbound drug from the liver water when blood flow, protein binding, and movement to the site of metabolism are not rate-limiting
kinetic model of CLH:

\[ CL_H = Q_H \frac{f_{ub} \cdot CL_u_{int}}{Q_H + f_{ub} \cdot CL_u_{int}} \]

describes the liver as a single, well-stirred compartment where unbound drug in the hepatic venous blood is in equilibrium with unbound drug in the liver.
Hepatic Clearance (CLH)
1. definition: volume of blood from which drug is completely removed by the liver per unit time
2. a function of hepatic blood flow (QH) and extraction ratio (ER)
   \[ CLH = QH \times ER \]
a. CLH can vary from 0 to QH (ER=1)

Three determinants of hepatic drug elimination
a. QH
b. protein binding (fub)
c. CLuint
## INTRINSIC CLEARANCE OF DRUGS

<table>
<thead>
<tr>
<th>High Clearance</th>
<th>Low Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>propranolol</td>
<td>antipyrine</td>
</tr>
<tr>
<td>lidocaine</td>
<td>warfarin</td>
</tr>
<tr>
<td>imipramine</td>
<td>theophylline</td>
</tr>
<tr>
<td>aldosterone</td>
<td>tolbutamine</td>
</tr>
<tr>
<td>hydrocortisone</td>
<td>diazepam</td>
</tr>
<tr>
<td>meperidine</td>
<td>phenylbutazone</td>
</tr>
<tr>
<td>phenacetin</td>
<td>phenytoin</td>
</tr>
<tr>
<td>propoxyphene</td>
<td></td>
</tr>
</tbody>
</table>
Two Compartment Models
Objectives:

• To understand the assumptions associated with the two compartment model
• Evaluate a biphasic concentration vs. time plot using the method of residuals following iv bolus administration
• To define, differentiate, calculate and understand the parameters, CL, Vc, V₂, distribution t₁/₂ and elimination t₁/₂ as they apply to a two compartment linear model
Many drugs given in a single intravenous bolus dose demonstrate a plasma level–time curve that does not decline as a single exponential (first-order) process. The plasma level–time curve for a drug that follows a two-compartment model shows that the plasma drug concentration declines biexponentially as the sum of two first-order processes; distribution and elimination. A drug that follows the pharmacokinetics of a two-compartment model does not equilibrate rapidly throughout the body, as is assumed for a one-compartment model. In this model, the drug distributes into two compartments, the central compartment and the tissue, or peripheral compartment.
Evidence

• Commonly we find with real data, especially if we have a number of early data points, that the log Cp versus time plot is not a straight line. We see an initial early deviation from the straight line, followed by a log-linear phase. The initial phase is a more rapid drop in plasma concentration before settling into the log-linear fall in plasma concentration.

• This suggests that the body is not behaving as a single well mixed compartment.
There appears, mathematically, to be distribution between two (or more) compartments. That is we don't have instantaneous equilibrium between the drug in all the various tissues of the body. In the next approximation we can consider that the body is behaving as two distinct compartments. These compartments can be called the central compartment and the peripheral compartment. Exact anatomical assignment to these compartments is not always possible. However, generally the rapidly perfused tissues often belong in the central compartment.
Assumptions

• 1-comp Linear Model
  – Rapidly equilibrate throughout the body.
• Rapid Mixing
  – Instantaneous and uniform distribution throughout the body.
• Linear Model
  – Drug elimination follows first order kinetics.

• 2-comp Linear Model
  – Does not rapidly equilibrate throughout the body.
• Rapid and Slow Mixing
  – Central compartment: instantaneous and uniform distribution (e.g. blood, extracellular fluid, and highly perfused tissues).
  – Peripheral compartment: relatively slow equilibration
• Linear Model
  – Drug distribution and elimination both follow first order kinetics.
Plasma Concentration-Time Course, iv Bolus

1-comp Linear Model

2-comp Linear Model
Plasma Concentration-Time Course, iv Bolus

1-comp Linear Model

\[ C = C(0) \cdot e^{-kt} \]

2-comp Linear Model

\[ C_{p,t} = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} \]

Jan 24, 2006

Two Comp iv bolus & infusion
Plasma Concentration-Time Course, iv Bolus

2-comp Linear Model

- Cp decreases in a biexponential manner with more rapid decrease during the distribution phase
- Elimination occurs during the distribution phase
- Distribution occurs during the elimination phase

\[ C_p = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} \]
Model A

Central compartment

\[ D_p \quad V_p \quad C_p \]

Tissue compartment

\[ D_t \quad V_t \quad C_t \]

\[ k_{12} \quad k_{21} \]

\[ k_{10} \]
Differential Equations

\[ \frac{dX_c}{dt} = K_{21}X_p - K_{12}X_c - K_{10}X_c \]

\[ \frac{dX_p}{dt} = K_{12}X_c - K_{21}X_p \]
Integrated Equation

\[ Cp = \frac{Xo(\alpha - K_{21})}{Vc(\alpha - \beta)} e^{-\alpha t} + \frac{Xo(K_{21} - \beta)}{Vc(\alpha - \beta)} e^{-\beta t} \]

\[ Cp = A \ e^{-\alpha t} + B \ e^{-\beta t} \]

\[ A = \frac{Xo(\alpha - K_{21})}{Vc(\alpha - \beta)} \]

\[ B = \frac{Xo(K_{21} - \beta)}{Vc(\alpha - \beta)} \]
\[ K_{21} = \frac{A\beta + B\alpha}{A + B} \]

\[ K_{10} = \frac{\alpha\beta}{K_{21}} \]

\[ K_{12} = \alpha + \beta - K_{21} - K_{10} \]
Drug in tissue compartment

\[ X_p = \frac{X_0 K_{12}}{(\alpha - \beta)} \left( e^{-\beta t} - e^{-\alpha t} \right) \]
2-Compartment Model, iv Bolus
Drug in Tissue (Peripheral) Compartment

Concentration (µg/mL)

Time (Hours)

0 12 24 36
Conc. Time Profile

\[ C_p = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} \]

\[ C_p = 24 \cdot e^{-1.5t} + 6 \cdot e^{-0.25t} \]

Slope (ln) \( \rightarrow \beta \)
Method of Residuals

\[ \alpha > \beta \]

slope (\( \ln \)) = \( \alpha \)
Calculation of PK-parameters

Volume of the Central Compartment

\[ V_C = \frac{X_0}{A + B} \]

Apparent Volume of Distribution

\[ V_\beta = \frac{K_{10}V_C}{\beta} \]
Fig. 19-4. Several events occur following a single i.v. bolus dose. A, Loss of drug from the initial dilution volume, of which plasma is a part, is due to both elimination from the body and distribution into the more slowly equilibrating tissues. The fall in amount of drug in the body is therefore initially less than the fall in the amount in the initial dilution volume. Only when distribution equilibrium has been achieved do the declines in the amounts in the initial dilution volume and in plasma parallel (same slope) that in the body. A, reflecting these events, the apparent volume of distribution (A/C), which just after giving the dose equals the initial dilution volume (V₁), increases with time approaching a limiting value (V), which occurs when distribution equilibrium is achieved.
The Volume of Dist. at Steady State

\[
V_{ss} = \frac{X_{ss}}{C_{ss}} = \left[ \frac{(K_{21} + K_{12})}{K_{21}} \right] \quad V_{c}
\]

Total Body Clearance

\[
Cl = \frac{X_0}{\int_{0}^{\infty} Cdt}
\]

\[
Cl = \beta \cdot V_{\beta} = K_{10}V_{c}
\]
Volumes of Dist.

\[
\text{Varea} > \text{Vss} > \text{Vc}
\]
Fig. 19-7. By approximately 1 hr into a 48-hr, constant-rate i.v. infusion of nicardipine (0.5 mg/hr), the plasma concentration has risen to 50% of the plateau value (14 μg/L) despite a terminal half-life of 12 hr. This rapid approach to plateau is a result of events in plasma being primarily controlled by an initial phase, with a half-life of 20 min, during which time significant elimination occurs following a bolus dose. The data are the means of 37 patients with mild-to-moderate hypertension (1 mg/L = 2.1 μM). (Redrawn from Cook, E., Clifton, G.G., Bienvenu, G., Williams, R., Sambol, N., McMahon, G., Grandy, S., Lai, C.-M., Quon, C., Anderson, C.R., Tulpapati, P., and Wallin, J.D. Pharmacokinetics, pharmacodynamics and minimum effective clinical dose of intravenous nicardipine. Clin. Pharmacol. Ther., 47:706–718, 1990.)
**Fraction of elimination associated with the terminal phase**

**Fig. 19–8.** Approach to plateau in plasma, during a constant-rate i.v. infusion, for a drug that displays biexponential disposition kinetics, is determined by the relative rates of distribution and elimination. In this example, the two exponential coefficients $\lambda_1$ and $\lambda_2$ are kept constant (with $\lambda_1 = 10\lambda_2$), and the fractional elimination term associated with the terminal phase, $f_2$, is varied from 0.01 to 1. When drug distributes rapidly compared with elimination ($f_2$ approaches 1), the terminal half-life controls the time to approach plateau. When $f_2$ is very low, e.g., 0.01, implying elimination occurs much faster than distribution, the approach to plateau is determined primarily by $\lambda_1$. Included for reference is the expected curve when the drug exhibits one-compartment characteristics ($f_2 = 1$), in which case 50% and 90% of the plateau are reached by 1 and 3.3 terminal half-lives, respectively. Note that time is expressed in units of terminal half-life.
Effective Half-Life in Clinical Pharmacology

Harold Boxenbaum, PhD, and Michele Battle, PhD

The concept of an "effective half-life" for drug accumulation was initially posited by Kwan and Duggan in 1977 and was formally examined in 1984. In principle, an effective half-life is one that reflects drug accumulation, as opposed to one or more aspects of exponential disposition. Unfortunately, this concept has not received wide acceptance. The purpose of this commentary is to discuss effective half-life in simple mathematical terms and thus stimulate its use in clinical pharmacology.

The concept of an effective half-life subsumes Wagner's accumulation factor, $R_c$. Accordingly, $R_c$ will initially be discussed, after which its relation to effective half-life will be examined. To simplify and focus the discussion, linear monoexponential disposition will initially be assumed.

WAGNER'S DRUG ACCUMULATION INDEX, $R_c$

Consider multiple-dose, intravenous bolus administration of a drug at equal intervals for which disposition is linearly monoexponential: let dose ($D$) = 100 mg, volume of distribution ($V$) = 1000 mL, disposition rate constant ($k$) = 0.11552453 hours$^{-1}$, disposition half-life ($t_{1/2}$) = 6 hours, and the constant dosing interval ($t$) = 6 hours. It may be demonstrated that under the conditions described above:

$$\frac{\text{AUC}_{\infty}}{\text{AUC}_{0-\infty}} = \frac{1}{1 - e^{-kt}} = \frac{1}{1 - 2^{-t/t_{1/2}}} = R_c$$

where $\text{AUC}_{\infty}$ is area under the plasma concentration-time curve over a steady-state dose interval, and $\text{AUC}(0-\infty)$ is area under the plasma concentration-time curve from 0 to $\infty$ hours following the first dose, and $R_c$ is the drug accumulation index. In this case, disposition half-life ($t_{1/2}$) = $ln(2)/k$ will always properly reflect drug accumulation. In this example and in all cases (bolus injection, monoexponential decay, linear system) in which bolus drug is administered at dose intervals equal to disposition half-life, the $R_c$ value will be 2, and accumulation will be two-fold (see Figure 1). If both dose and dosage interval are doubled (i.e., daily dose remains unchanged), $R_c = 1.33$; hence, $R_c$ is regimen dependent.

Next, consider the same input-disposition model, but in a somewhat more generalized sense. In a series of cases of intravenous infusions, 100 mg of the drug is administered at a constant rate over periods ranging from 1 minute (i.e., a bolus) to 6 hours. Figure 2 illustrates the resulting plasma concentration-time profiles over the time frame of 0 to 6 hours. Note that as infusion duration becomes more prolonged, $\text{AUC}(0-6)$ becomes progressively smaller. However, since dose and $t$ remain constant (100 mg every 6 hours), $AUC_{\infty}$ remains unaffected; namely, $\text{AUC}_{\infty} = \text{Dose/Clearance}$. Referring to equation 1, it is apparent that the slower the input, the smaller $\text{AUC}(0-6)$ will be, and the larger $R_c$ will be. Once again, we note that $R_c$ is regimen (e.g., input rate) dependent. In fact, one could take advantage of this property by conducting simulations using various input functions, thereby investigating the impact of input on drug accumulation, namely $R_c$.

EFFECTIVE HALF-LIFE

Inasmuch as effective half-life was created to reflect accumulation with respect to $R_c$, it must change in...
Dosage calculations

- Dosage calculations are complicated by the extra terms in the equations. However some calculations are still reasonably straightforward. The dose required for a particular initial plasma concentration can be calculated if $V_c$ is known. Thus: $\text{DOSE} = V_c \times C_{po(\text{required})}$
- To achieve an initial $C_p$ of 20 mg/L given $V_1 = 30$ liter would require a $\text{DOSE} = 20 \times 30 = 600$ mg.
- Alternately if a dose of 500 mg is given and the $V_1$ value is 16 L, the expected $C_{po0}$ can be calculated. $C_{po} = 500/16 = 31.3$ mg/L
continuous IV infusion

- The SS plasma concentration achieved after a continuous IV infusion is given by the same equation described for the one compartment model, i.e.:-

\[ K_0 = C_{pss} \times \text{clearance} = C_{pss} \times V_1 \times k_{el} \]

- If a plasma concentration of 30 mg/L is required and \( V_1 = 15 \) L and \( k_{el} \) is 0.2 hr\(^{-1}\) then the required infusion rate can be readily determined.

\[ K_0 = 30 \times 15 \times 0.2 = 90 \text{ mg/hr} \]
Fig. 2.10 Decline in plasma levels of a drug that confers two-compartment model characteristics on the body, following constant rate intravenous infusion to steady state (—) and following the rapid intravenous injection of a dose that gives an initial drug concentration equal to the steady-state concentration (-----). The biexponential characteristic of the drug is more evident following the bolus injection than after terminating the infusion.
Oral administration
Oral - Two Compartment with Distribution Phase

\[ A = 20 \text{ mg/L}; \ B = 15 \text{ mg/L}; \]
\[ \alpha = 1 \text{ hr}^{-1}; \ \beta = 0.1 \text{ hr}^{-1}; \]
\[ k_a = 2 \text{ hr}^{-1} \]
Oral - Two Compartment Plot without Distribution Phase

Concentration, mg/L

A = 20 mg/L; B = 15 mg/L; alpha = 1.5 hr$^{-1}$; beta = 0.16 hr$^{-1}$; ka = 1 hr$^{-1}$

Time, hr
100 mg of a drug was administered by rapid IV injection to a 70-kg, healthy adult male. Blood samples were taken periodically after the administration of drug, and the plasma fraction of each sample was assayed for drug. The following data were obtained:

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Plasma Concentration (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>43.00</td>
</tr>
<tr>
<td>0.5</td>
<td>32.00</td>
</tr>
<tr>
<td>1.0</td>
<td>20.00</td>
</tr>
<tr>
<td>1.5</td>
<td>14.00</td>
</tr>
<tr>
<td>2.0</td>
<td>11.00</td>
</tr>
<tr>
<td>4.0</td>
<td>6.50</td>
</tr>
<tr>
<td>8.0</td>
<td>2.80</td>
</tr>
<tr>
<td>12.0</td>
<td>1.20</td>
</tr>
<tr>
<td>16.0</td>
<td>0.52</td>
</tr>
</tbody>
</table>
Table 4.3 Application of the Method of Residuals

<table>
<thead>
<tr>
<th>TIME (hr)</th>
<th>$C_p$ Observed Plasma Level</th>
<th>$C'_p$ Extrapolated Plasma Concentration</th>
<th>$C_p - C'_p$ Residual Plasma Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>43.0</td>
<td>14.5</td>
<td>28.5</td>
</tr>
<tr>
<td>0.5</td>
<td>32.0</td>
<td>13.5</td>
<td>18.5</td>
</tr>
<tr>
<td>1.0</td>
<td>20.0</td>
<td>12.3</td>
<td>7.7</td>
</tr>
<tr>
<td>1.5</td>
<td>14.0</td>
<td>11.0</td>
<td>3.0</td>
</tr>
<tr>
<td>2.0</td>
<td>11.0</td>
<td>10.0</td>
<td>1.0</td>
</tr>
<tr>
<td>4.0</td>
<td>6.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.0</td>
<td>2.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.0</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.0</td>
<td>0.52</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[
C_p = 45e^{-1.8t} + 15e^{-0.21t}
\]
<table>
<thead>
<tr>
<th>Drug</th>
<th>Beta Half-Life</th>
<th>Distributional Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>1.8 hr</td>
<td>8 min</td>
</tr>
<tr>
<td>Cocaine</td>
<td>1 hr</td>
<td>18 min</td>
</tr>
<tr>
<td>Theophylline</td>
<td>4.33 hr</td>
<td>7.2 min</td>
</tr>
<tr>
<td>Ergometrine</td>
<td>2 hr</td>
<td>11 min</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>3 hr</td>
<td>14.7 min</td>
</tr>
<tr>
<td>Milrinone</td>
<td>3.6 hr</td>
<td>4.6 min</td>
</tr>
<tr>
<td>Procainamide</td>
<td>2.5–4.7 hr</td>
<td>6 min</td>
</tr>
<tr>
<td>Quinidine</td>
<td>6–8 hr</td>
<td>7 min</td>
</tr>
<tr>
<td>Lithium</td>
<td>21.39 hr</td>
<td>5 hr</td>
</tr>
<tr>
<td>Digoxin</td>
<td>1.6 days</td>
<td>35 min</td>
</tr>
<tr>
<td>Human FSH</td>
<td>1 day</td>
<td>60 min</td>
</tr>
<tr>
<td>IgG1 kappa MAB</td>
<td>9.6 days (monkey)</td>
<td>6.7 hr</td>
</tr>
</tbody>
</table>
1) A drug has a distribution that can be described by a two-compartment open model. If the drug is given by IV bolus, what is the cause of the initial or rapid decline in blood levels (α phase)? What is the cause of the slower decline in blood levels (β phase)?
2) A drug that follows a multicompartment pharmacokinetic model is given to a patient by rapid intravenous injection. Would the drug concentration in each tissue be the same after the drug equilibrates with the plasma and all the tissues in the body? Explain.
3) The pharmacokinetics of amrinone after a single IV bolus injection (75 mg) in 14 healthy adult male volunteers followed a two-compartment open model and fit the following parameters:

\[ A = 4.62 \pm 12.0 \, \mu g/mL \]
\[ B = 0.64 \pm 0.17 \, \mu g/mL \]
\[ \alpha = 8.94 \pm 13 \, hr^{-1} \]
\[ \beta = 0.19 \pm 0.06 \, hr^{-1} \]

From these data, calculate:

a. The volume of the central compartment
b. The volume of the tissue compartment
c. The transfer constants \( k_{12} \) and \( k_{21} \)
d. The elimination rate constant from the central compartment
e. The elimination half-life of amrinone after the drug has equilibrated with the tissue compartment
\[ C_P = Ae^{-at} + Be^{-bt} \]

After substitution,
\[ C_P = 4.62e^{-8.94t} + 0.64e^{-0.19t} \]

a. \[ V_P = \frac{D_0}{A + B} = \frac{75,000}{4.62 + 0.64} = 14,259 \text{ mL} \]

b. \[ V_t = \frac{V_Pr_{12}}{r_{21}} = \frac{(14,259)(6.52)}{(1.25)} = 74,375 \text{ mL} \]

c. \[ r_{12} = \frac{AB(b - a)^2}{(A + B)(Ab + Ba)} \]
\[ k_{12} = \frac{(4.62)(0.64)(0.19 - 8.94)^2}{(4.62 + 0.64)[(4.62)(0.19) + (0.64)(8.94)]} \]

\[ k_{12} = 6.52 \text{ hr}^{-1} \]

\[ k_{21} = \frac{Ab + Ba}{A + B} = \frac{(4.62)(0.19) + (0.64)(8.94)}{4.62 + 0.64} \]

\[ k_{21} = 1.25 \text{ hr}^{-1} \]

d. \[ k = \frac{ab(A + B)}{Ab - Ba} = \frac{(8.94)(0.19)(4.62 + 0.64)}{(4.62)(0.19) + (0.64)(8.94)} \]

\[ = 1.35 \text{ hr}^{-1} \]
4) Some clinical pharmacists assume that, at steady state when equilibration is reached between the plasma and the tissue, the tissue drug concentration would be the same as the plasma. Do you agree?