Important Concepts

- **Absorption**
  - peak levels, loading dose, volume of distribution, bioavailability.

- **Elimination by 1st order kinetics**
  - linear pharmacokinetics, exponential decay, half-life, clearance.

- **Steady state drug levels**
  - drug accumulation, maintenance dose, maximum and minimum drug levels with intermittent dosing.

- **Complications**
  - distribution phase, non-linear or zero-order pharmacokinetics, plasma protein binding.

- **Varying goals for therapeutic drug monitoring (TDM)**
  - use of peak versus trough (and random) drug levels.
Critical Information

- For the drug:
  - Rate of absorption, distribution and $V_d$.
  - Clearance (Cl) and/or half-life ($t_{1/2}$).
  - Relative roles of hepatic metabolism and renal elimination.
  - Reference range and recommended indices for TDM.

- For the patient:
  - Weight (sometimes height, gender and race too).
  - Drug History (including dosages, recent changes, previous drug levels, etc.).
  - Clinical Status (including liver and renal function and signs of drug efficacy/toxicity).
Only Three Critical Equations

1) \[ [\text{drug}]_{\text{peak}} = \frac{\text{dose}}{V_d} \]
   - Relates the peak drug level to a single dose and the volume of distribution \((V_d)\).
   - Also quantitates the total amount of drug in the body at any time based upon the serum drug level.

2) \[ [\text{drug}]_{\text{steady state}} = \frac{\text{rate}_{\text{in}}}{\text{Cl}} \]
   - Relates the steady state drug level to the “infusion rate” and the clearance \((\text{Cl})\) for a drug eliminated by 1st order or linear pharmacokinetics.

3) \[ \text{Cl} = \left(0.693 \times V_d\right) / t_{1/2} \]
   - Relates clearance \((\text{Cl})\) to half-life \((t_{1/2})\) and the volume of distribution \((V_d)\).
   - Fyi only: \(\text{Cl} = k \times V_d\), where \(k\) is the exponential rate constant for elimination and \(k = 0.693 / t_{1/2} = 1 / \tau_c\).
Simplified Pharmacokinetics

steady state = \( \frac{\text{Rate}_{\text{in}}}{\text{Cl}} \)

bolus = \( \frac{\text{(single dose)}}{V_d} \)

\( t_{\text{max}} = \text{steady state} + \frac{1}{2} \times \text{bolus} \)

\( t_{\text{min}} = \text{steady state} - \frac{1}{2} \times \text{bolus} \)
Critical Importance of the Half-life!

- Half life is the key for knowing
  - When a new medication is started, how long until the patient reaches steady state?
  - When a patient stops taking a medication, how long until it is gone?
  - When a drug dosage is changed, how long until a new steady state is achieved?
Critical Importance of the Half-life!

1 \cdot t_{1/2} = 50% \\
2 \cdot t_{1/2} = 75% \\
3 \cdot t_{1/2} = 87.5% \\
4 \cdot t_{1/2} = 93.75% \\
5 \cdot t_{1/2} = 96.875%
Case 1: Theophylline Overdose

- A 23 y.o., 90 kg female is seen in the ED approximately 2 hours after ingesting 50 (estimated) of her brother’s Theo-Dur (300 mg theophylline) tablets.

- She is alert and oriented with a HR=110, RR=20, and a temp=99.7 F. EKG shows sinus tachycardia.
Case 1: Theophylline Overdose

- We start by looking up pharmacokinetic parameters on theophylline:
  - Therapeutic Range: 5 – 20 mg/L
    - N/V, Anxiety, Nervousness seen >20 mg/L
    - Tachycardia begins at between 20 – 40 mg/L
    - Arrhythmias can be seen >40 mg/L
    - Seizures can be seen >50 mg/L
  - Vd = 0.5 L/kg; 100% bioavailable, time to peak after P.O. administration ~ 1 – 2 hours, distribution rapid.
  - Clearance = 0.04 L/hr/kg or t₁/₂ ~ 8.3 hours
**Case 1: Theophylline Overdose**

- A serum theophylline level is measured at 33 mg/L

- Although elevated, the measured theophylline level is not critical and probably doesn’t support an admission.

- Additionally, the patient only displays signs sinus tachycardia, which is consistent with a serum level less than 40 mg/dL.

- So, is this patient medically cleared to be discharged home?
Case 1: Theophylline Overdose

- No, first we should estimate her peak plasma level assuming instantaneous and complete absorption of all the ingested tablets.
  - \[ \text{peak} = \frac{\text{dose}}{V_d} \]
  - \[ \text{peak} = \frac{(50 \times 300 \text{ mg})}{(0.5 \text{ L/kg} \times 90 \text{ kg})} = 333 \text{ mg/L} \]
- This is much higher than the initial measured theophylline level of 40 mg/L.
Case 1: Theophylline Overdose

- At 2 hours post-ingestion of a therapeutic dose, we would be expecting a peak level. However, the measured level is much lower than the predicted peak. Why?
  
  - Delayed absorption due to formations of concretions, delayed gastric emptying and mucosal irritation.
  
  - When absorption is delayed, then significant elimination can occur during absorption limiting the peak drug level and the overall “AUC” (area under the curve).
  
  - The estimated dosage (50 tabs) may be too high.
  
  - Also, vomiting frequently occurs following theophylline overdose.
Case 1: Theophylline Overdose

- Can the patient be considered medically clear at this time?
  - I hope this answer is relatively obvious: NO.
  - Probably warrants an ICU/CCU admission with serial theophylline levels and close cardiac monitoring until levels peak and then finally start to decrease.
  - Use of charcoal hemoperfusion and/or hemodialysis to enhance elimination might be warranted.
Case 2: Chronic Lithium Overdose

- 67 year old female with a history of bipolar disorder is brought in by her daughter due to “difficulty seeing and walking”.

- Takes lithium 300 mg bid (twice per day) with her last lithium level six months ago at 1.1 mEq/L.

- Also started taking ibuprofen regularly (“a few pills at a time”) for joint pain a few months ago.

- On review of systems patient reports weight gain, blurred vision, loose stools, slight tremor, weakness in arms and legs, and drowsiness.

- Blood sample is drawn with a lithium level of 3.2 mEq/L (therapeutic range of 0.5 – 1.2 mEq/L).
Case 2: Chronic Lithium Overdose

- After discussion with the patient and family, it becomes clear that she has been taking her regular dosage of lithium and this is not an intentional overdose.

- Further lab tests reveal she has moderate renal insufficiency.

- How do you think this developed?

- Lithium is 100% cleared through the kidneys. Decreased renal function means decreased lithium clearance. Without a compensatory change in her daily dosage this resulted in her lithium level slowly increasing to a new (toxic) steady state.
Case 2: Chronic Lithium Overdose

- Assuming the patient is admitted and not given any additional lithium, how long would it take for her serum level to decrease to < 1.0 mmol/L?

- Calculate clearance: \([\text{drug}]_{\text{steady state}} = \frac{\text{rate}_{\text{in}}}{\text{Cl}}\)
  - \(\text{rate}_{\text{in}} = \frac{(300 \text{ mg/12 hours})}{(6.9 \text{ mg/mmol})} = 3.6 \text{ mmol/hr}\)
  - \(\text{Cl} = \frac{(3.6 \text{ mmol/hr})}{(3.2 \text{ mmol/L})} = 1.1 \text{ L/hr}\)

- Convert \(\text{Cl}\) to \(t_{1/2}\): \(\text{Cl} = \frac{(0.693 \times V_d)}{t_{1/2}}\)
  - \(t_{1/2} = \frac{(0.693 \times 0.6 \text{ L/kg} \times 70 \text{ kg})}{(1.1 \text{ L/hr})} = 26.5 \text{ hrs}\)

- Hence, in a little more than two days, she should decrease from 3.2 to 1.6 to 0.8 mmol/L.
Case 2: Chronic Lithium Overdose

- Should we worry whether the level used to calculate half-life is closer to the peak or trough?
- Why isn’t she more toxic?
- How to treat?
  - Monitor carefully while lithium clears (could consider hemodialysis).
  - Hydrate to improve renal perfusion; hold ibuprofen.
Case 3: Initiating Pharmacotherapy

- 15 year old male with tonic-clonic seizures (85 kg) is started on 500 mg Levetiracetam PO bid (twice a day).

- What are his expected approximate peak and trough levels?
  - Therapeutic Range: 5 – 30 mg/L
  - \( V_d \sim 0.6 \text{ L/kg} = 0.6 \text{ L/kg} \times 85 \text{ kg} = 51 \text{ L} \)
  - \( t_{1/2} \sim 7 \text{ hours} \)
    - Clearance = \( (0.693 \times V_d) / t_{1/2} = 5 \text{ L/hr} \)
Approximate (easy) Solutions for 500 mg bid

\[ [\text{bolus}] = \frac{\text{(single dose)}}{V_d} \]
\[ = \frac{500 \text{ mg}}{51 \text{ L}} = 9.8 \text{ mg/L} \sim 10 \text{ mg/L} \]

\[ [\text{steady state}] = \frac{\text{Rate}_{\text{in}}}{\text{Cl}} \]
\[ = \frac{1000 \text{ mg/24 hrs}}{5 \text{ L/hr}} = 8.3 \text{ mg/L} \sim 8 \text{ mg/L} \]

\[ [\text{max}] = [\text{steady state}] + \frac{1}{2} \times [\text{bolus}] \]
\[ = 8 \text{ mg/L} + (0.5 \times 10 \text{ mg/L}) = 13 \text{ mg/L} \]

\[ [\text{min}] = [\text{steady state}] - \frac{1}{2} \times [\text{bolus}] \]
\[ = 8 \text{ mg/L} - (0.5 \times 10 \text{ mg/L}) = 3 \text{ mg/L} \]
Comparison of Approximate and Exact Calculations for Steady State Min and Max

Approximate (easy) Solutions

\[ \text{bolus} = \frac{\text{single dose}}{V_d} = \frac{500 \text{ mg}}{51 \text{ L}} = 9.8 \text{ mg/L} \]

\[ \text{steady state} = \frac{\text{Rate}_{\text{in}}}{C_l} = \frac{1000 \text{ mg/24 hrs}}{5 \text{ L/hr}} = 8.3 \text{ mg/L} \]

\[ \text{max} = \text{steady state} + \frac{1}{2} \times \text{bolus} = 8 \text{ mg/L} + (0.5 \times 10 \text{ mg/L}) = 13 \text{ mg/L} \]

\[ \text{min} = \text{steady state} - \frac{1}{2} \times \text{bolus} = 8 \text{ mg/L} - (0.5 \times 10 \text{ mg/L}) = 3 \text{ mg/L} \]

Exact (more complicated) Solutions

\[ \text{bolus} = \frac{\text{single dose}}{V_d} = \frac{500 \text{ mg}}{51 \text{ L}} = 9.8 \text{ mg/L} \]

\[ \text{max} = \text{bolus} / \{1 - \exp(-0.693*\tau/t_{1/2})\} = 9.8 \text{ mg/L} / (1 - 0.304) = 14.1 \text{ mg/L} \]

\[ \text{min} = \text{max} \times \exp(-0.693*\tau/t_{1/2}) = 14.1 \text{ mg/L} \times 0.304 = 4.3 \text{ mg/L} \]
Case 3: Initiating Pharmacotherapy

- Our patient is told to take one 500 mg levetiracetam (Keppra) tablet in the morning and one in the late evening for two days and then on the third morning go have a blood sample drawn just before he takes his morning dose (i.e. a trough level, and > 5 half-lives have passed).

- Levetiracetam level comes back the next day at 2.2 mg/L (low).

- The patient’s family reports a couple of early evening seizures (why?).

- Dose is doubled to 1000 mg bid.
  - Remember that due to “linear pharmacokinetics”, trough and peak levels should also double due to the increased dose (at steady state).
  - i.e., troughs around 4 – 5 mg/L and peaks around 25 – 30 mg/L.
Case 3: Initiating Pharmacotherapy

- After a few more days, another trough level is measured at 5.5 mg/L.
- Patient is kept at this dose, but after a few weeks he begins to have occasional seizures, which could be a result of tolerance.
- Dose is again raised to 1500 mg bid.
Case 3: Initiating Pharmacotherapy

- After a few weeks at 1500 mg bid, seizures are well controlled but patient is having difficulty performing at school, especially during his morning classes.

- He reports dizziness, difficulty concentrating, and nausea with occasional vomiting.

- What is going on?
Approximate (easy) Solutions for 1500 mg bid

- bolus = \((single\ dose) / V_d\) = 1500 mg / 51 L = 29.4 mg/L
- steady state = \(\text{Rate}_{in} / Cl\) = (3000 mg/24 hrs) / (5 L/hr) = 25 mg/L
- max = steady state + \(\frac{1}{2} \times\) bolus = 25 mg/L + (0.5 * 29 mg/L) = 39.5 mg/L
- min = steady state - \(\frac{1}{2} \times\) bolus = 25 mg/L - (0.5 * 29 mg/L) = 10.5 mg/L
Case 3: Initiating Pharmacotherapy

- Patient probably requires a minimum level of 10 mg/L to suppress seizures, but at the current dosing regimen experiences serious side effects at peak levels approaching 40 mg/L.

- What is the solution?
  - Lowering the total daily dose might make the patient more susceptible to seizures.
  - Alternative is to divide the 3000 mg into three daily doses of 1000 mg each.
Approximate (easy) Solutions for 1000 mg tid

\[ [\text{bolus}] = \frac{\text{single dose}}{V_d} \quad = \frac{1000 \text{ mg}}{51 \text{ L}} = 19.6 \text{ mg/L} \sim 20 \text{ mg/L} \]

\[ [\text{steady state}] = \frac{\text{Rate}_{\text{in}}}{\text{Cl}} \quad = \frac{3000 \text{ mg/24 hrs}}{5 \text{ L/hr}} = 25 \text{ mg/L} \]

\[ [\text{max}] = [\text{steady state}] + \frac{1}{2} \times [\text{bolus}] \quad = 25 \text{ mg/L} + (0.5 \times 20 \text{ mg/L}) = 35 \text{ mg/L} \]

\[ [\text{min}] = [\text{steady state}] - \frac{1}{2} \times [\text{bolus}] \quad = 25 \text{ mg/L} - (0.5 \times 20 \text{ mg/L}) = 15 \text{ mg/L} \]
Case 3: Initiating Pharmacotherapy

• At 1000 mg tid, patient should maintain levels above ~ 15 mg/L, which should be therapeutic, but will still might peak (depending on rate of absorption) above 30 mg/L (upper limit of therapeutic range).

• Possible solutions?
  – A dosing schedule of 750 mg tid works well, but impractical.
  – Recommend taking pills on a full stomach to delay absorption and also limit peak levels (due to ongoing elimination during absorption).
  – Switch to an extended release tablet (if available).
  – Can sometimes add a 2nd medication with synergistic benefits (but not synergistic toxicities), allowing each to be given at lower doses.
Case 4: Gentamicin Dosing

- 70 kg patient with normal renal function started on 2 mg/kg (140 mg) gentamicin PO q8h.
- What are the expected approximate peak and trough levels?
  - Gentamicin Therapeutic Range:
    - Peak: 5 – 10 µg/ml
    - Trough: <2 µg/ml
  - Gentamicin $V_d \sim 0.2 \text{ L/kg} = 0.2 \times 70 \text{ L} = 14 \text{ L}$
  - Gentamicin $t_{1/2} \sim 2$ hours
    - $Cl = (0.693 \times V_d) / t_{1/2} = 4.85 \text{ L/h}$
- Notice right away that $t_{1/2} << \tau$, the dosing interval.
Predicted peak and trough levels?

Approximate (easy) Solutions

\[
\begin{align*}
[\text{bolus}] &= \frac{\text{(single dose)}}{V_d} = 140 \text{ mg} / 14 \text{ L} = 10 \mu \text{g/ml} \\
[\text{steady state}] &= \frac{\text{Rate}_{\text{in}}}{\text{Cl}} = \frac{(140 \text{ mg} / 8 \text{ hrs})}{(4.85 \text{ L/hr})} = 3.61 \mu \text{g/ml} \\
[\text{max}] &= [\text{steady state}] + \frac{1}{2} * [\text{bolus}] = 3.61 \mu \text{g/ml} + 0.5 * 10 \mu \text{g/ml} = 8.61 \mu \text{g/ml} \\
[\text{min}] &= [\text{steady state}] - \frac{1}{2} * [\text{bolus}] = 3.61 \mu \text{g/ml} - 0.5 * 10 \mu \text{g/ml} = -1.4 \mu \text{g/ml}
\end{align*}
\]

- The above numbers clearly don’t make sense, so we think for a moment...
- What they are telling us is that each gentamicin dose peaks around 8.6 μg/ml and then is nearly completely eliminated before the next dose (~4 half-lives later).
Varying Goals of TDM

1) Maintain drug levels within the therapeutic range (e.g. phenytoin or digoxin).

2) Maintain drug level above some minimally effective level (e.g. vancomycin and the “MIC”), with or without avoiding toxic (high) levels.

3) For some antibiotics (e.g. gentamicin) efficacy is best measured using a peak level (due to “peak-dependent killing” and the “post-antibiotic effect”) and toxicity is avoided by making sure the trough levels fall below a certain threshold (toxicity due to chronic accumulation).

4) Most complicated situation is where only the “area under the curve” (AUC) correlates with either efficacy or toxicity and the pharmacokinetics are not predictable (e.g. cyclosporine).
   - a combination of trough and peak levels are most commonly used

5) As long as the total dose is adequate, drug monitoring is not necessary (e.g. penicillin).
   - generally applies when EITHER a drug has a very wide therapeutic range/index OR has very predictable pharmacokinetics
Case 5: Final Dosing Example

- 45 year old female (65 kg) recovering from recent neurosurgery for resection of glioma has occasional seizures.

- Started on phenobarbital 100 mg bid.

- Phenobarbital PK Parameters
  - >95% bioavailable, orally absorbed < 2 hours and rapidly distributed, Vd ~ 0.55 L/kg.
  - Hepatic metabolism with t_{1/2} ~ 60 hrs.
  - Inactive metabolites eliminated renally.
  - Therapeutic range: 15 – 30 mg/L.
Case 5: Final Dosing Example

- After two days on 100 mg bid, physicians checks a trough blood level:
  - $[\text{Phenobarbital}] = 10 \text{ mg/L}$

- Since this is about $\frac{1}{2}$ of the desired trough level, physician raises the dose to 200 mg bid.

- However, a week later the patient returns with signs of toxicity. A level drawn at that time is 41 mg/L.
  - This is a fourfold increase, but the dose was only doubled.
  - What happened?
Approximate (easy) Solutions for 100 mg bid (based on 60 hr $t_{1/2}$)

\[ [\text{bolus}] = \frac{\text{(single dose)}}{V_d} = \frac{100 \text{ mg}}{36 \text{ L}} = 2.8 \text{ mg/L} \sim 3 \text{ mg/L} \]

\[ [\text{steady state}] = \frac{\text{Rate}_{in}}{\text{Cl}} = \frac{200 \text{ mg/24 hrs}}{0.4 \text{ L/hr}} = 20.8 \text{ mg/L} \sim 21 \text{ mg/L} \]

\[ [\text{max}] = [\text{steady state}] + \frac{1}{2} \times [\text{bolus}] = 21 \text{ mg/L} + (0.5 \times 3 \text{ mg/L}) = 22.5 \text{ mg/L} \]

\[ [\text{min}] = [\text{steady state}] - \frac{1}{2} \times [\text{bolus}] = 21 \text{ mg/L} - (0.5 \times 3 \text{ mg/L}) = 19.5 \text{ mg/L} \]

Steady State (avg) had dose not been changed.

When first level was drawn.

\[ [\text{bolus}] \]

\[ [\text{max}] \]

\[ [\text{min}] \]

\[ t_{1/2} \]
Approximate (easy) Solutions for 200 mg bid (based on 60 hr \( t_{1/2} \))

\[
\text{[bolus]} = \frac{\text{single dose}}{V_d} = \frac{200 \text{ mg}}{36 \text{ L}} = 5.6 \text{ mg/L} \sim 6 \text{ mg/L}
\]

\[
\text{[steady state]} = \frac{\text{Rate}_{\text{in}}}{Cl} = \frac{400 \text{ mg/24 hrs}}{0.4 \text{ L/hr}} = 41.6 \text{ mg/L} \sim 42 \text{ mg/L}
\]

\[
\text{[max]} = \text{[steady state]} + \frac{1}{2} \times \text{[bolus]} = 42 \text{ mg/L} + (0.5 \times 6 \text{ mg/L}) = 45 \text{ mg/L}
\]

\[
\text{[min]} = \text{[steady state]} - \frac{1}{2} \times \text{[bolus]} = 42 \text{ mg/L} - (0.5 \times 6 \text{ mg/L}) = 39 \text{ mg/L}
\]

~42.0 mg/L after 5 \( t_{1/2} \)

New steady state after dose is doubled.
Case 6: Acute Digoxin Overdose

- 63 y.o., 60 kg female is brought to the ED 30 minutes after ingesting 25 x 0.25 mg digoxin tabs.

- Patient complains of nausea, but is otherwise asymptomatic.

- Physical examination is normal except for an irregular heart beat around 76 beats/min with BP of 130/85.

- ECG shows controlled atrial fibrillation.
Brief Overview of Digoxin Toxicity

• Extracardiac symptoms:
  • fatigue, visual disturbances, weakness, nausea, anorexia, abdominal pain, dizziness, headache, diarrhea, vomiting.

• Cardiac signs:
  • Bradycardia, tachycardia, atrial flutter, atrial fibrillation, A-V block, PVCs, ventricular fibrillation and arrest

• Other:
  • hyperkalemia and seizures
Estimation of the peak plasma digoxin level:

- \([\text{digoxin}]_{\text{peak}} = \frac{(\text{Dose})}{(\text{Vd})}\)

  - Assume normal renal function and a
    - \(V_d \sim 5 \text{ L/kg} = 5 \text{ L/kg} \times 60 \text{ kg} = 300 \text{ L}\)

  - Hence, (digoxin is 70% orally bioavailable)
    - \([\text{digoxin}]_{\text{peak}} = (0.7)(25 \times 250 \mu g)/300 \text{ L}\)
    - \([\text{digoxin}]_{\text{peak}} = 14.6 \mu g/L\)

  - Note that this peak level has been predicted for the **fully distributed state**.
Acute Digoxin Overdose

- **Initial laboratory values:**
  - Plasma digoxin level of **16 µg/L** (0.5 – 2.0)
  - Potassium: 3.9 mM (3.5 – 4.5), Cr: 0.7 mg/dL (0.5 – 1.2)
- Therapeutic range for digoxin is 0.5 – 2.0 µg/L.
- Signs of cardiac toxicity should be evident by EKG above 3 µg/L. Cardiac arrhythmias become increasingly likely as the level increases above this level.
- This patient is mildly tachycardic but has a normal sinus rhythm. Why?
Digoxin has a classic distribution phase that complicates interpretation of:

- It has only been approximately 1 hour since ingestion.
- Absorption is going to be greatly delayed and distribution is still ongoing.
- Toxicity is only reflected by the concentration of drug in the final compartment.
- Note that with a final predicted level of 14.6 μg/L, we might expect an initial peak level of 146 μg/L. However, due to slow absorption this will never be actually realized.
- Hence, it is necessary to treat immediately and follow patient clinically for signs of toxicity.