Theophylline Overdose

- A 23 y.o., 90 kg female is seen in the ED ~2 hours after ingestion of 50 of her brother's Theo-Dur (300 mg theophylline) tablets.
- She is alert and oriented with a HR=110 bpm, RR=20 bpm, and a temp=99.7 F. EKG shows sinus tachycardia.
- A serum theophylline level is 33 mg/L.

Theophylline Overdose

- We start by looking up pharmacokinetic paramaters 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.
  - Clearance = 0.04 L/hr/kg or $t_{1/2}$ ~ 8.3 hours

Theophylline Overdose

- Although elevated, the measured theophylline level of 33 mg/dL is not critical and probably doesn't support an admission.
- Additionally, the patient only displays signs sinus tachycardia, consistent with a serum level less than 40 mg/dL.
- So, it this patient medically cleared to be discharged home?

Theophylline Overdose

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

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 level. 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”.
  - Also, vomiting frequently occurs following theophylline administration.

Theophylline Overdose

- How would immediate treatment strategies affect the pharmacokinetics of theophylline?
  - Activated charcoal and whole-bowel irrigation will decrease ***bioavailability***.
  - Multiple-dose activated charcoal (targeting enterohepatic recirculation), charcoal hemoperfusion and hemodialysis increase the ***elimination rate*** and decrease the ***half-life***.

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 would be a clinical decision.

Pentobarbital Case Example

- A patient receives a continuous infusion of pentobarbital (a short-acting barbiturate) for 3 straight days.
- The infusion is terminated, but the patient has not awakened after 6+ hours.
- However, the reported duration of action of pentobarbital after a single IV dose is 1 – 4 hours maximum.
- What is the explanation?

Pentobarbital Case Example

- The short duration of action of “short-acting” barbiturates is NOT due to a rapid elimination rate; it is due to a slow redistribution.
- After a short-acting barbiturate is administered, it rapidly distributes into an initial water-soluble compartment where it acts on the CNS.
- The barbiturate then redistributes from this water-soluble volume to a much larger lipid-soluble compartment, where it is sequestered from acting on the CNS. The overall concentration of the barbiturate is much lower in this larger volume.
- The barbiturate is then slowly eliminated from the lipid-soluble compartment with a half-life of 15 – 48 hours. During this elimination phase the serum level never becomes high enough to affect the CNS similar to its initial effect.

Pentobarbital Case Example

- In this case, because the barbiturate was infused continuously over 3 days, drug accumulation occurred and the lipid-soluble phase became very concentrated with drug.
- This resulted in a high barbiturate concentration in the serum in equilibrium with the lipid-soluble volume.
- Hence, during the slow elimination phase the high serum barbiturate level directly acts on the CNS. It may take days for this patient to awaken.

Digoxin Case Example

- 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 patient's peak plasma digoxin level:

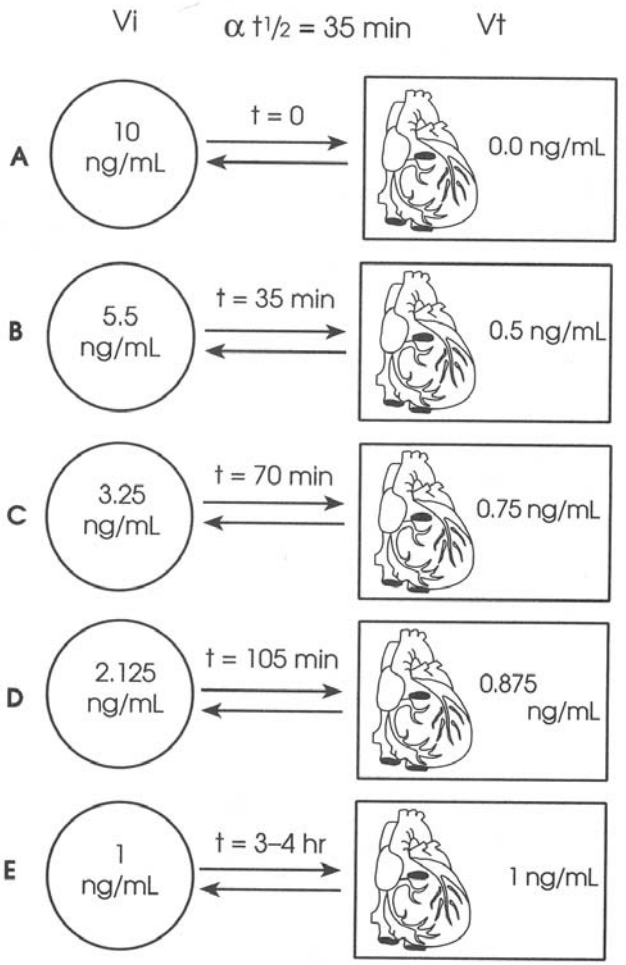
- $[digoxin]_{bolus} = (F)(Dose)/(Vd)$
- Assume normal renal function and a
  - $V_d \sim 5$ L/kg = 5 L/kg * 60 kg = 300 L
- Hence,
  - $[digoxin]_{bolus} = (0.7)(25*250\ \mu g)/300$ L
  - $[digoxin]_{bolus} = 14.6\ \mu g/L$
- Note that this peak level has been predicted for the fully distributed state.

Digoxin Case Example

- 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 mildy tachycardic but has a normal sinus rhythm. Why?

Digoxin has a classic distribution phase that complicates interpretation of early levels.

- 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.



Methanol Overdose

- A 70 kg man with a history of alcoholism ingests an unknown amount of methanol. His serum methanol level is 100 mg/dL.
- The following information is available.
  - Mol. Wt. of methanol = 32 daltons.
  - Ethanol and methanol have a specific gravity of 0.8 g/mL.
  - The V_d of both ethanol and methanol is 0.6 L/kg.
  - The bioavailability of ethanol and methanol is 100%.
  - Ethanol and methanol have no protein-binding in the serum.
  - The V_{max} for ethanol elimination is 0.15 g/kg/hr or 25 mg/dL/hr, but varies between 13 – 30 mg/dL/hr.

Methanol Overdose

- Assuming 100 mg/dL is a peak level, how much methanol did the patient drink?
  - $[]_{peak}$ = dose / V_d
  - dose = $[]_{peak}$ * V_d = 100 mg/dL * 10 dL/L * 0.6 L/kg * 70 kg
  - dose = 42 g of pure methanol.
- Assuming the patient drank anti-freeze which is 95% methanol, estimate the volume consumed.
  - 42 g / (0.8 g/ml) = 52.5 ml of 100% methanol
  - 52.5 ml / 0.95 = 55.3 ml of the anti-freeze.

Methanol Overdose

- Treatment requires a serum ethanol concentration of 100 mg/dL to block metabolism of the methanol to formic acid. Calculate an appropriate loading dose of 100% ethanol in volume:
  - dose = $[]_{peak}$ * V_d = (100 mg/dL * 10 dL/L)*(0.6 L/kg * 70 kg)
  - dose = 42 g / (0.8 g/mL) = 52.5 mL of 100% ethanol.
  - Generally administered IV as 10% ethanol; hence would need to infuse 525 mL.
- What if all you have on hand is vodka?
  - Vodka is generally 40% ethanol.
  - 52.5 mL / 0.4 = 131.25 ml of vodka (PO).

Methanol Overdose

- Calculate the appropriate maintenance dose of 10% ethanol to achieve a steady state level of 100 mg/dL.
  - Steady state requires **$amount_{in} = amount_{out}$**
  - Hence, all we need to do is replace the amount eliminated (assuming an initial appropriate loading dose).
  - Using a V_{max} = 0.15 g/kg/hr, a 70 kg man would be expected to eliminate 10.5 g ethanol per hour.
  - 10.5 g/hr / (0.8 g/ml) = 13.1 ml/hr of ethanol or 131 ml/hr of 10% ethanol (v/v).
- Note that because elimination rates are so variable between individuals, ethanol therapy requires frequent ethanol levels and adjustments of the maintenance dose.
  - Although Fomepizole is much more expensive than ethanol, it doesn't require this close monitoring and has effectively replaced use of ethanol for treatment of methanol and ethylene glycol poisonings.

Methanol Overdose

- Lastly, we ask how many hours of hemodialysis are required to lower the serum methanol level from 100 mg/dL to 10 mg/dL?
  - Hemodialysis is a first-order process and has a clearance of 150 mL/min for methanol.
  - $Cl = (0.693 * V_d) / t_{1/2}$
  - $t_{1/2} = (0.693 * 0.6\ L/kg * 70\ kg) / (150\ mL/min * 10^{-3}\ L/mL) =$ 194 minutes or ~3.2 hours
  - Count half-lives:
    - 100 → 50 → 25 → 12.5 → 6.25
    - between 3 – 4 half-lives (closer to 3) or about **10 hours**

Free Phenytoin Example

- An ICU patient has an unexpectedly low total [phenytoin] = 6 mg/L, despite an appropriately calculated loading dose.
- The ICU resident calls and asks if there could be a problem with our assay.
- We notice that the patient has a very low albumin of 1.5 g/L.
- How do we advise them on interpreting this low total phenytoin level?

Free Phenytoin Example

- There are actually multiple approaches, but they all rely on initially calculating an appropriate ***correction factor (f)*** for the low albumin:
  - Simple method: f = 1.5 / 4 = 0.375
  - Better equation: f = (0.2 * 1.5) + 0.1 = 0.4 (*Sheiner-Tozer*)
- Method 1: Calculate a corrected reference range for total phenytoin.
  - 0.4 * ("standard ref range") = "corrected ref range"
  - 0.4 * (10 – 20 mg/L) = 4 – 8 mg/L
- Method 2: Calculate a corrected total phenytoin.
  - $[\text{phenytoin}]_{\text{total,corr}}$ = (6 mg/L) / 0.4 = 15 mg/L
- Method 3: Calculate a predicted free phenytoin.
  - $[\text{phenytoin}]_{\text{free,predicted}} = 0.1/0.4 * [\text{phenytoin}]_{\text{total,measured}}$
  - $[\text{phenytoin}]_{\text{free,predicted}}$ = 0.1/0.4 * 6 mg/L = 1.5 mg/L
- Note that all three of the above methods demonstrate that the patient is precisely in the middle of the standard reference range.

Digoxin Case Example #2

- B.G., a 62 y.o., 50 kg female, with CHF who was admitted for possible digoxin toxicity.
- She has been taking 0.25 mg of digoxin daily for many months.
- Her serum Cr is 3.0 mg/dl.
- On admission, her plasma digoxin level is 4.0 μg/L (reference range 0.5 – 2.0 μg/L).
- If digoxin adminstration is stopped immediately, how long will it take for her plasma level to fall from 4.0 to 2.0 μg/L?

Digoxin Case Example #2

- The simple answer is “one half-life”; however, how long is a half-life in this case?
- First, we need to know how digoxin is eliminated:
  - ~50/50 metabolic/renal, $Cl_{dig} = Cl_{met} + Cl_{renal}$
  - Cl_{dig} (ml/min) = (0.8)(wt in kg) + (Cl_{Cr} in ml/min)
  - Cl_{dig}CHF (ml/min) = (0.33)(wt in kg) + (0.9)(Cl_{Cr} in ml/min)
  - Cl_{Cr} for Males (ml/min) = (140 – Age)(wt in kg) / (72*Cr)
  - Cl_{Cr} for Females (ml/min) = (0.85)(140 – Age)(wt in kg) / (72*Cr)
- Interestingly, digoxin V_d is also dependent on weight and renal function:
  - V_d digoxin (L) = (3.8 L/kg)(wt in kg) + (3.1)(Cl_{Cr} in ml/min)
  - Alternatively, V_d = 6-7 L/kg with normal renal function and 4-6 L/kg in chronic renal failure.

Digoxin Case Example #2

- Estimation of the half-life requires one of our "memorized" equations: $t_{1/2} = (0.693*V_d)/Cl_{dig}$
- We have two options for estimating this patient's digoxin clearance (Cl_{dig}):
  - We can assume steady state (expect for dosing interval to be shorter than the half-life) and estimate it from another of our "memorized" equations: $Digoxin_{SS} = rate_{in} / Cl_{dig}$
  - Or, we can use the more complicated equations for Cl_{dig} from the previous slide.
  - As will be demonstrated on next slide, the two methods give equivalent results (in this case).

Digoxin Case Example #2

Calculated based on Serum Cr

- Cl_{Cr} = (0.85)(140 – Age)(Wt) / (72*Cr)
- Cl_{Cr} = (0.85)(140 – 62)(50) / (72*3.0)
- Cl_{Cr} = 15.3 ml/min
- $Cl_{dig} = Cl_{metab} + Cl_{renal}$
- Cl_{dig} = (0.33)(wt) + (0.9)(Cl_{Cr})
- Cl_{dig} = (0.33)(50) + (0.9)(15.3)
- Cl_{dig} = 30.3 ml/min

Based on $[digoxin]_{steady\ state}$

- Cl_{dig} = (F)(dose/time) / ($[dig]_{ss}$)
- Cl_{dig} = (0.7)(250 μg/24 hrs) / (4.0 μg/L)
- Cl_{dig} = 1.82 L/hr
- Cl_{dig} = (1.82 L/hr)(1000 ml/L) / (60 min/hr)
- Cl_{dig} = 30.4 ml/min
- Cl_{dig} = 43.8 L/day

Digoxin Case Example #2

- We now have sufficient data to estimate the half-life of digoxin in this patient: $t_{1/2} = (0.693*V_d)/Cl_{dig}$
- We need to calculate the V_d for digoxin:
  - V_d digoxin (L) = (3.8 L/kg)(wt in kg) + (3.1)(Cl_{Cr} in ml/min)
  - V_d digoxin (L) = (3.8 L/kg)(50 kg) + (3.1)(15.3 ml/min)
  - V_d digoxin = 237 L
- Alternatively, a more rough estimate of Vd that does not require calculation of Cl_{Cr} is ~ 6-7 L/kg for normal renal function and 4-6 L/kg for chronic renal failure:
  - V_d digoxin = 50 kg * 4-6 L/kg = 200 – 300 L

Digoxin Case Example #2

- Remember, $t_{1/2} = (0.693*V_d)/Cl_{dig}$
- Hence, $t_{1/2}$ = (0.693*237 L)/(43.8 L/day) = 3.75 days with the more precise calculation.
- Or, $t_{1/2}$ = (0.693*[200-300] L)/(43.8 L/day) = 3.2 – 4.7 days with the rough estimation of V_d.
- Therefore, it will take about 4 days for the patient's digoxin level to fall from 4.0 to 2.0 μg/L.

Phenytoin Overdose

- A 70 kg male is admitted with a serum phenytoin level of 80 mg/L. Assume the ingestion occurred two days earlier and there is no ongoing absorption or distribution.

- How long will it take for the patient's phenytoin level to fall to 20 mg/L?

Phenytoin Overdose

- Remember that phenytoin switches from first order to zero order pharmacokinetics across a clinically significant range.
- For most patients the Michaelis-Menton constant (K_m) for phenytoin elimination is around 4 mg/L.
- Hence, we can make a rough assumption that the rate of elimination is nearly maximal during this entire period.
- V_{max} ~ 7 mg/kg/day for phenytoin.

Phenytoin Overdose

- Given a V_{max} ~ 7 mg/kg/day, a 70 kg patient will eliminate 490 mg/day.
- The V_d for phenytoin is around 0.7 L/kg, or 49 L for a 70 kg patient.
- With zero-order pharmacokinetics, knowledge of the body weight isn't really necessary. The elimination rate can be expressed as
  - (7 mg/kg/day)/(0.7 L/kg) = 10 mg/L per day.
- Hence, it will take about 6 days for patient's level to fall from 80 mg/L to 20 mg/L.

Phenytoin Overdose

- For enzymatic metabolism, it is possible to use classical “Michaelis-Menton” mechanics to calculate rates of elimination:
  - $dC/dt = (V_{max}/V_d)*C/(K_m+C)$, where C is the serum phenytoin concentration.
- After integration and solving for “t”, we come up with an equation for estimating how long it takes to reach a specific drug concentration:
  - $t = [K_m(\ln C_1/\ln C_2) + (C_1 – C_2)] / (V_{max}/V_d)$
- For this case, this equation predicts that it will take 6.55 days for the phenytoin level to decrease from 80 mg/L to 20 mg/L