Pharmacogenetic Case Example

HPI:  56 y.o. female, 140 lbs., presents with bleeding gums, epistaxis, and bloody stools. Also describes excessive fatigue and mild chest pain on exertion.

PMH: Previously diagnosed with psoriasis and put on azathioprine (100 mg/day PO) about one month ago.

Lab:  Hct 18%, Hb 6, WBC 800, Platelets 1,000: “Pancytopenia” – all blood cell levels strongly suppressed.
Role of TPMT in Metabolism of 6-thiopurine (6-TP) Medications

Both *efficacy* and *toxicity* are dependent on the level of 6-TGNs.
Inter-individual Heterogeneity in TPMT Activity Recognized by Weinshilboum over 20 Years Ago.

Weinshilboum and Sladek
Relationship between Inherited Variations in TPMT Activity and Serum Levels of (active) 6-TGNs

Krynetski and Evans
*Pharm Res* 16(3):342-9, 1999
6-TP TDM and TPMT Testing

• Before 6-TP drugs are started, TPMT genotype and/or RBC TPMT activity can be assessed and used to guide 6-TP dosage.

• During treatment, RBC 6-MP, 6-MMP and 6-TGN levels can be measured to guide therapy.
Pharmacogenetics

• Interindividual genetic variation in either
  – Drug Response (receptors, targets, etc.)
  – Drug Metabolism

• Important current examples include, 6-thiopurines, irinotecan, warfarin, succinylcholine and 5-fluorouracil.

• Good Reference Sites
  – http://www.pharmgkb.org/
The Osmolal Gap

- Osmolality should be measured using freezing point depression (normal range: 275 – 295 mOsm/kg H₂O).
- Calculated osmolality estimated using
  \[ Osm_{estimated} = 2*[Na] + [BUN]/2.8 + [Glucose]/18 \]
- Osmolal Gap = \( Osm_{measured} - Osm_{estimated} \)
- Normal range ~ -5 to + 10 mOsm/kg H₂O
- The gap is a small difference between two large numbers and hence is very sensitive to any variations or inaccuracies in the measurements.
  - Must be based upon measurements from a single blood draw
Causes of an Increased Serum Osmolal Gap

I. Real

- Requires a large amount of a small (i.e. not a macromolecule), neutral molecule.
- There are really only three classes of molecules that cause an elevated osmolal gap and can achieve a significant circulating level (without causing instant death):
  i. Alcohols (and acetone)
  ii. Glycols
  iii. Neutral Sugars (e.g. mannitol, sorbitol, glycerol)
      (very rarely DMSO – rather toxic)

II. Artifact

- Not from a single blood draw!
- Artifactual hyponatremia due decreased serum free water from hyperproteininemia or hypertriglycerideridemia (can be corrected by measuring a “whole blood ionized” Na).
- Other unexpectedly high cations such as hypermagnesemia.
Relationship between osmolality and alcohol/glycol level

- Osmolality is in units of milliOsmoles per kg (or liter) of “free” water (note that serum and plasma contain ~ 93% free water).

- Alcohols and glycols are measured as milligrams per deciliter (mg/dL) of serum or plasma.

- Empirical conversion factors can be estimated as (Mol.Wt. / 10) * 0.93 {mg/dL per each 1 mOsm/kg H₂O}
  - Methanol  3.0
  - Ethanol   4.3
  - Ethylene Glycol  5.8
  - Acetone  5.4
  - Isopropanol  5.6
  - Propylene Glycol  7.1
Caution: The osmolal gap is NOT a sensitive screen for toxic exposure!

• Anything over 25 mg/dl of ethylene glycol is considered severely toxic and hemodialysis is recommended.

• An ethylene glycol of 25 mg/dl contributes only \(~4 \text{ mOsm/kg}\) to the osmolal gap.

• Most people have a osmolal gap around 1 – 3 mOsm/kg (although there is a wide spread of normal values, up to 10 mOsm/kg).

• Hence, most people ingesting 25 mg/dl of ethylene glycol will still have a normal osmolal gap \((3 + 4 = 7)\).

• For this reason, a normal osmolal gap does NOT rule out a toxic alcohol/glycol ingestion. On the other hand, a high gap does raise the suspicion of a toxic ingestion.

• Bottom line is that the BEST thing to do is to test for both alcohols and glycols whenever a reasonable clinical suspicion exist.

• Similarly, if a patient has clearly tested negative for both alcohols and glycols, yet still appears to have an elevated osmolal gap, it is probably due to a non-toxic cause (DKA is an example).
Unexplained Osmolal Gap

• 35 y.o. woman brought to YNHH ED who reportedly drank a “few beers” and ingested a bottle of pills about an hour ago.

• Patient is awake and alert, although slightly inebriated, and has no ‘focal’ neurological signs/symptoms. Physical exam unremarkable, except for an increased respiratory rate.

• What is the significance of the increased respiratory rate?
  – ABG revealed a respiratory alkalosis. What drugs can cause this?
  – Progesterone, Methylxanthines, Salicylates, Catecholamines and Nicotine
# Immunoassay Results

## Urine DAU panel
- Barbiturate - NEG
- Opiates - NEG
- Methadone - NEG
- Benzodiazepine - NEG
- Cocaine - NEG
- Amphetamine - NEG
- PCP - NEG

## “Serum” Overdose panel
- Salicylates - POS
  - 48 mg/dl
- Acetaminophen - NEG
- Barbiturates - N/P
- Alcohol - POS
  - Ethanol @ 146 mg/dl
- TCA - N/P
Osmolal Gap

• Measured serum osmolality = 341 mOsm/kg H₂O.
• Calculated serum osmolality = 
  \[(2 \times 140) + \left(\frac{8}{2.8}\right) + \left(\frac{115}{18}\right) = 289\] mOsm/kg H₂O.
• Osmolal Gap = 341 – 289 = 52 mOsm/kg H₂O.
• Contribution of Ethanol to the osmolal gap
  \[= \frac{146}{4.3} = 34\] mOsm/kg H₂O.
• Unexplained osmolal gap
  \[= 52 – 34 = 18\] mOsm/kg H₂O.
• What should they do?
Test for Glycols by GC

• Ethylene glycol undetected.
• Propylene glycol = 120 mg/dl (high)
• Explains Osmolal Gap of 18 mOsm/Kg H₂O:
  – 120 mg/dl / 7.1 = 17 mOsm/kg H₂O.
• Source?
  – Iatrogenic: IV, PO medications (including oral activated charcoal!)
• Dangerous?
  – Not normally. Converted to lactic acid and liver has a large metabolic capacity to convert lactic acid into alanine via the Cori cycle.
  – Follow serum lactic acid levels for caution.
Propylene Glycol Metabolism

Pathway 1

Propylene glycol $\xrightleftharpoons{}$ Lactaldehyde $\rightarrow$ Methylglyoxal $\rightarrow$ Lactic acid

Pathway 2

Propylene glycol phosphate $\rightarrow$ Acetyl phosphate $\rightarrow$ Lactaldehyde phosphate $\rightarrow$ Lactyl phosphate $\rightarrow$ Lactic acid
Iatrogenic Intoxication

• 54 y.o. man admitted to a CT hospital for Ethanol withdrawal. Given 1 g Ativan IV q6 hrs.

• Became unresponsive over next ~10 hours and required intubation due to respiratory depression. Transferred to ICU.

• During evaluation detected an osmolal gap of 144.

• Sample sent to YNHH for glycol testing.
  – Propylene glycol = 810 mg/dl

• Cause?
  – IV Ativan contains 4 mg/ml lorazepam in 80% propylene glycol. 1 g Ativan would require 250 ml * 0.8 = 200 ml propylene glycol exposure over 6 hours.
  – (200 ml*1.04 g/ml*10^3 mg/g) / (Vd=70kg*0.58 L/kg*10 dl/L)=512 mg/dl
DKA or alcohol ingestion?

• 35 year old woman with a history of poorly-controlled type 1 diabetes and alcohol dependence presents with severe stupor, lethargy and smell of acetone on breath.

• On physical examination, the patient was
  – afebrile, with BP 125/65, HR 85 bpm, and RR 16,
  – lungs CTA, cardiac RRR no G/M/Rs,
  – funduscopic examination was unremarkable,
  – and a neurologic examination showed no evidence of focal deficits.
Initial Laboratory Values

• Na 138, K 4.0, Cl 108, HCO$_3^-$ 22
• Anion Gap = 138 – (108 + 22) = 8 (normal)
• BUN 10, Cr 1.2, **Glucose 350**, Lactate 1.6
• Serum Ethanol < 10 mg/dl (enzymatic method)
• ABG: pH 7.35, PaO2 81, PCO2 35
  – (meant to represent a very mild acidosis)
• Urinalysis revealed positive “ketones”.
• CT scan of the head and lumbar puncture normal.
Additional Laboratory Values

• Serum Osmolality = 326 mOsm/kg H₂O
• Calculated Osmolality (Na, BUN, Glc)
  = 299 mOsm/kg H₂O.
• Osmolal Gap
  = 326 – 299 = 27 mOsm/kg H₂O.

• Blood sample sent to outside lab for comprehensive alcohol/glycol panel by GC.
What to do?

- Diabetic ketoacidosis not likely with glucose of 350 and lack of acidosis.
- Ketosis without significant acidosis argues against a toxic ingestion with either methanol or ethylene glycol.
- Degree of stupor cannot be explained by ethanol ingestion and considering the presence of an elevated osmolal gap and ketosis, must suspect isopropanol ingestion.
- However, very important to distinguish isopropanol from ethylene glycol or methanol ingestion (if possible) due to important question of whether or not to give ethanol drip or fomepizole (contraindicated with isopropanol).
- Isopropanol treatment is purely supportive with possible use of hemodialysis.
- If a comprehensive alcohol/glycol panel is not available, patient should be followed closely for signs of acidosis. Can also consider presumptive treatment for ethylene glycol/methanol poisoning (fomepizole or ethanol drip).
- Eventually, an isopropanol of 55 mg/dl and an acetone of 45 mg/dl was reported.
A cardiac surgeon calls with a reported alcohol level on his patient, whom he suspects is a closet alcoholic. Whether or not he is hiding his alcoholism will determine his ability to undergo cardiac transplant due to the complicated treatment and physiologic demands post-operatively.

The patient came in for a scheduled CT scan at 6:00 AM and was reported to be appearing “drunk” and behaving combatively.

Upon confrontation by the surgeon many hours later he admits to having been “out” with friends the night before but swears he only had a couple of beers.

At 11:00 AM, a serum ethanol level was measured at 49 mg/dl (all other alcohols and glycols negative).

The surgeon wants to know (1) how drunk is 49 mg/dl and (2) can you calculate how drunk he was at 6 AM?
<table>
<thead>
<tr>
<th>Serum Ethanol Level (mg/dL)</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 mg/dl</td>
<td>Mild muscular incoordination</td>
</tr>
<tr>
<td>50-100</td>
<td>Incoordination; driving increasingly dangerous</td>
</tr>
<tr>
<td>100-150</td>
<td>Mood, personality, behavioral changes; driving is dangerous</td>
</tr>
<tr>
<td>150-200</td>
<td>Prolonged reaction time; driving is very dangerous</td>
</tr>
<tr>
<td>200-300</td>
<td>Nausea, vomiting, diplopia, marked ataxia</td>
</tr>
<tr>
<td>300-400</td>
<td>Hypothermia, dysarthria, amnesia</td>
</tr>
<tr>
<td>400-700</td>
<td>Coma, respiratory failure, death</td>
</tr>
</tbody>
</table>
Ethanol Metabolism

Ethanol is eliminated by zero-order pharmacokinetics.

- Implies a constant rate of elimination regardless of ethanol concentration due to saturation of the metabolizing enzymes (ADH, etc.).

- Strictly follow Michaelis-Menten mechanics with a $K_m < 5$ mg/dl. This means that assumption of zero-order behavior is reliable down to clinically insignificant blood levels.

- 15-20 mg/dL/hr in nondrinkers

- 30-40 mg/dL/hr in habitual drinkers
Calculations

11:00 AM: \[ \text{[EtOH]} = \frac{49 \text{ mg/dl}}{1217} = 0.04\% \text{ (w/w)} \]

Minimal metabolism:
5 hrs*15 mg/dl/hr = 75 mg/dl + 49 mg/dl = 124 mg/dl

\[
\frac{124 \text{ mg/dl}}{1217} = 0.10 \% \text{ (w/w)}
\]

More likely metabolism:
5 hrs*30 mg/dl/hr = 150 mg/dl + 49 mg/dl = 199 mg/dl

\[
\frac{199 \text{ mg/dl}}{1217} = 0.16 \% \text{ (w/w)}
\]

Definitely Drunk!
Iatrogenic Intoxication

- 54 y.o. man admitted to a CT hospital for Ethanol withdrawal. Given 1 g Ativan IV q6 hrs.
- Became unresponsive over next ~10 hours and required intubation due to respiratory depression. Transferred to ICU.
- During evaluation detected an osmolal gap of 144.
- Sample sent to YNHH for glycol testing.
  - Propylene glycol = 810 mg/dl
- Cause?
  - IV Ativan contains 4 mg/ml lorazepam in 80% propylene glycol. 1 g Ativan would require 250 ml * 0.8 = 200 ml propylene glycol exposure over 6 hours.
  - \( \frac{(200 \text{ ml} \times 1.04 \text{ g/ml} \times 10^3 \text{ mg/g})}{(V_d=70\text{ kg} \times 0.58 \text{ L/kg} \times 10 \text{ dl/L})} = 512 \text{ mg/dl} \)
An ugly technical complication.

• 55 y.o. man with a history of leukemia (unspecified at the moment) found obtunded after an apparent suicide attempt. An empty pill bottle is found on the bedside.

• On physical exam, patient is minimally arousable, afebrile, BP 110/60, HR 65, RR 14, with 3 mm pupils (unresponsive to light) and decreased bowel sounds.
Laboratory Values

- Na 123, K 3.4, Cl 100, HCO$_3^-$ 20
- Anion Gap = 123 – (95 + 20) = 8
- Glc 105, BUN 18, Cr 1.9, Lactate 2.6
- Serum overdose panel: Acetaminophen, Salicylates, Barbiturates, Alcohol Panel and TCAs are ALL negative.
- Urine Drugs of Abuse Panel: Opiates – POS, all the rest are negative.
- Serum osmolality: 315 mOsm/kg H$_2$O.
- Calculated osmolality: 268 mOsm/kg H$_2$O.
- Osmolal Gap: 315 – 268 = 47 mOsm/kg H$_2$O.
Significance of Osmolal Gap?

• Do we suspect alcohol/ethylene glycol ingestion?
• Note that the calculated osmolality is low and the measured osmolality is only slightly elevated.
  – This is not typical with an alcohol or glycol ingestion where the gap should be due purely to an increase in measured osmolality.

• So, what else could cause this?
  – An error or bad draw (mixed samples)?
  – Artifactual hyponatremia?
What type of leukemia was that?

• Answer: multiple myeloma.
• Oh, okay; that explains it...
• When the total protein is very high (as in myeloma) there are artifactually low measured electrolytes.
• This is because the body regulates the molality of electrolytes but we measure the molarity.
  – Protein free solution bathes cells (B&B)
• Plasma is normally only 93% free water. Therefore, molality and molarity normally only differ by about 7% (molal values are higher).
• When the protein concentration is much higher, there is a “volume exclusion” effect such that although the molality of the electrolytes is maintained the molarity decreases.
Correction for Volume Exclusion

• Plasma water can be estimated:

\[
\text{plasma water [g/dl]} = 99.1 - 0.73*P_s - 1.03*L_s
\]

\(P_s\) and \(L_s\) are serum protein and lipid, respectively, in g/dl).

• Normal plasma water is \(~93\) g/dl for a total protein of 8 g/dl and total lipid around 0.6 g/dl

• This patient had a total protein of 24 g/dl and a normal lipid profile (0.6 g/dl), which gives a plasma free water of 81 g/dl.

• We can calculate a “corrected” Na:

\[
\text{Na(corrected to normal } P_s,) = 123 * (93/81) = 141.
\]

• We are also able to measure the true molality of Na in whole blood using an ion-selective electrode on undiluted blood, but this must also be corrected to 93 g/dl plasma water. In this case, we got a perfectly matching Na of 141 mM.
What does this mean for the osmolal gap?

• All of the analytes in the calculated osmolality are subject to the same analytical artifact and should be corrected similarly.

• Hence, we take our previous calculated osmolality of 268 and multiply it by 93/81 to get a corrected calculated osmolality of 308 mOsm/kg H₂O.

• As the measured osmolality is truly a “molal” quantity (as it is based on the physical property of freezing point depression), the previously measured value of 315 mOsm/kg H₂O is accurate.

• Hence, the corrected osmolal gap is actually

  \[ 315 - 308 = 7 \text{ mOsm/kg H}_2\text{O}. \]

  **Although the patient is truly hyperosmolar (probably due to renal failure), there is no osmolal gap.**
Relation between the clinical ethanol level and the legal “BAC”

• Clinically, we measure the serum (or plasma) alcohol concentration (in mg/dl) as it gives the best correlation with pharmacologic effect.

• Unfortunately, forensic alcohol levels are defined as the **percentage** of ethanol (by weight) in **whole blood** (either weight or volume, depending on the State).

• So, how do these values compare?
First step:
relating mg/dl to “%(w/w or w/v)”

<table>
<thead>
<tr>
<th>mg EtOH</th>
<th>dl serum</th>
<th>1 ml serum</th>
<th>1 g serum</th>
<th>100 % (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dl serum</td>
<td>100 ml serum</td>
<td>~ 1 g serum</td>
<td>1000 mg serum</td>
<td>mg EtOH/mg serum</td>
</tr>
</tbody>
</table>

Hence, a measured alcohol level in mg/dl can be converted to %(w/w) by dividing by 1000. Equivalently, division by 1000 is used for conversion to %(w/v).

For example, a serum ethanol of 100 mg/dl is equivalent to 0.1 %(w/w or w/v) in serum.

However, note that this conversion is from serum to serum and we need to convert from serum to whole blood.
Second step: relating relating *serum* to *whole blood*

- In whole blood, alcohol partitions unequally between plasma and RBCs (more in serum).
- There is a significant, unpredictable variability in this partition [see Rainey, PM (1993), *Clinical Chemistry*, 39(11), 2288].
- Geometric mean for the serum:blood ratio of 1.15 with a 95% confidence interval of 1.14 – 1.17 (relates to w/v).
Putting it together

• To predict the median BAC in %(w/v) from the measured serum alcohol level in mg/dl, divide by 1150 (1000 * 1.15).

• To predict the median BAC in %(w/w) from the measured serum alcohol level in mg/dl, divide by 1217 (1150 * 1.058 - where 1.058 represents the median density of whole blood).
The Legal Implications

<table>
<thead>
<tr>
<th>Probability</th>
<th>100 mL of blood (w/v)</th>
<th>100 g of blood (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50% (more likely than not)</td>
<td>115&lt;sup&gt;a&lt;/sup&gt;</td>
<td>122</td>
</tr>
<tr>
<td>&gt;95% (reasonable medical certainty)</td>
<td>140</td>
<td>149</td>
</tr>
<tr>
<td>&gt;99% (beyond a reasonable doubt)</td>
<td>149</td>
<td>159</td>
</tr>
</tbody>
</table>

<sup>a</sup> Concentrations (mg/dL) based on the data reported here. To convert values in mg/dL to mmol/L, multiply by 0.217.
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 #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 administration 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, $\text{Cl}_{\text{dig}} = \text{Cl}_{\text{met}} + \text{Cl}_{\text{renal}}$
  - $\text{Cl}_{\text{dig}}$ (ml/min) = (0.8)(wt in kg) + ($\text{Cl}_{\text{Cr}}$ in ml/min)
  - $\text{Cl}_{\text{dig}}$ CHF (ml/min) = (0.33)(wt in kg) + (0.9)($\text{Cl}_{\text{Cr}}$ in ml/min)
  - $\text{Cl}_{\text{Cr}}$ for Males (ml/min) = (140 – Age)(wt in kg) / (72*Cr)
  - $\text{Cl}_{\text{Cr}}$ 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)($\text{Cl}_{\text{Cr}}$ 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: \( t_{1/2} = \frac{0.693*V_d}{C_{\text{ldig}}} \)

- We have two options for estimating this patient’s digoxin clearance (\( C_{\text{ldig}} \)):
  - 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: \( \text{Digoxin}_{SS} = \frac{\text{rate}_{in}}{C_{\text{ldig}}} \)
  - Or, we can use the more complicated equations for \( C_{\text{ldig}} \) 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**
- \( \text{Cl}_{\text{Cr}} = (0.85)(140 - \text{Age})(\text{Wt}) / (72*\text{Cr}) \)
- \( \text{Cl}_{\text{Cr}} = (0.85)(140 - 62)(50) / (72*3.0) \)
- \( \text{Cl}_{\text{Cr}} = 15.3 \text{ ml/min} \)
- \( \text{Cl}_{\text{dig}} = \text{Cl}_{\text{metab}} + \text{Cl}_{\text{renal}} \)
- \( \text{Cl}_{\text{dig}} = (0.33)(\text{wt}) + (0.9)(\text{Cl}_{\text{Cr}}) \)
- \( \text{Cl}_{\text{dig}} = (0.33)(50) + (0.9)(15.3) \)
- \( \text{Cl}_{\text{dig}} = 30.3 \text{ ml/min} \)

**Based on \([\text{digoxin}]_{\text{steady state}}\)**
- \( \text{Cl}_{\text{dig}} = (F)(\text{dose/time}) / ([\text{dig}]_{\text{ss}}) \)
- \( \text{Cl}_{\text{dig}} = (0.7)(250 \mu\text{g}/24 \text{ hrs}) / (4.0 \mu\text{g}/\text{L}) \)
- \( \text{Cl}_{\text{dig}} = 1.82 \text{ L/hr} \)
- \( \text{Cl}_{\text{dig}} = (1.82 \text{ L/hr})(1000 \text{ ml/L}) / (60 \text{ min/hr}) \)
- \( \text{Cl}_{\text{dig}} = 30.4 \text{ ml/min} \)
- \( \text{Cl}_{\text{dig}} = 43.8 \text{ L/day} \)
Digoxin Case Example #2

- We now have sufficient data to estimate the half-life of digoxin in this patient: $t_{1/2} = (0.693*V_d)/\text{Cl}_{\text{dig}}$

- We need to calculate the $V_d$ for digoxin:
  - $V_d \text{ digoxin (L)} = (3.8 \text{ L/kg})(\text{wt in kg}) + (3.1)(\text{Cl}_{\text{Cr in ml/min}})$
  - $V_d \text{ digoxin (L)} = (3.8 \text{ L/kg})(50 \text{ kg}) + (3.1)(15.3 \text{ ml/min})$
  - $V_d \text{ digoxin} = 237 \text{ L}$

- Alternatively, a more rough estimate of Vd that does not require calculation of $\text{Cl}_{\text{Cr}}$ is ~ 6-7 L/kg for normal renal function and 4-6 L/kg for chronic renal failure:
  - $V_d \text{ digoxin} = 50 \text{ kg} * 4-6 \text{ L/kg} = 200 – 300 \text{ L}$
Digoxin Case Example #2

• Remember, \( t_{1/2} = \frac{(0.693 \times V_d)}{Cl_{dig}} \)

• Hence, \( t_{1/2} = \frac{(0.693 \times 237 \text{ L})}{(43.8 \text{ L/day})} = 3.75 \text{ days} \) with the more precise calculation.

• Or, \( t_{1/2} = \frac{(0.693 \times [200-300] \text{ L})}{(43.8 \text{ L/day})} = 3.2 - 4.7 \text{ days} \) 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 \( \mu \text{g/L} \).
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-Menten 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.

• $V_{\text{max}} \sim 7$ mg/kg/day for phenytoin.
Phenytoin Overdose

• Given a $V_{\text{max}} \sim 7 \text{ mg/kg/day}$, 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
  - $(7 \text{ mg/kg/day})/(0.7 \text{ L/kg}) = 10 \text{ mg/L per day}$.

• 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:
  – $\frac{dC}{dt} = \frac{(V_{\text{max}}/V_d) \cdot C}{(K_m + C)}$, 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:
  – $t = \frac{K_m (\ln C_1/\ln C_2) + (C_1 - C_2)}{(V_{\text{max}}/V_d)}$

• 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