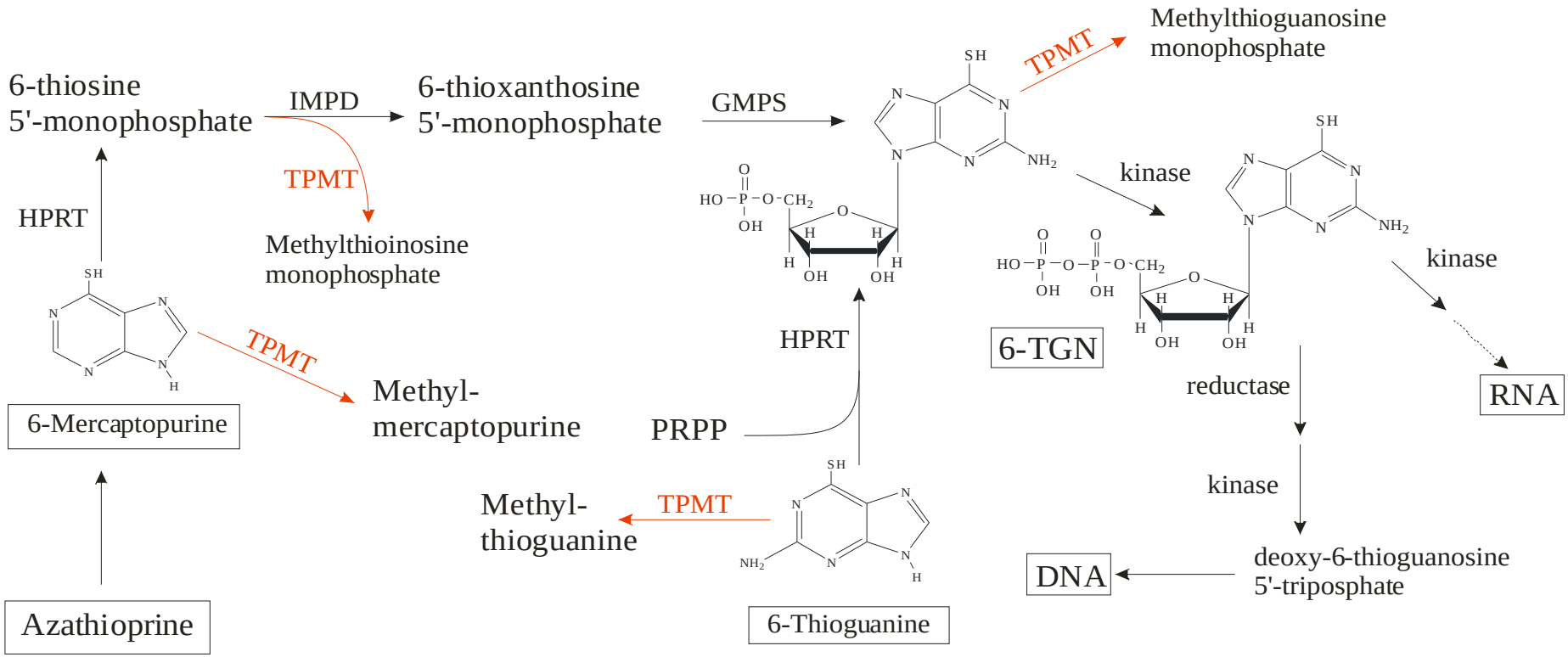
Pharmacogenetic Case Example

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.

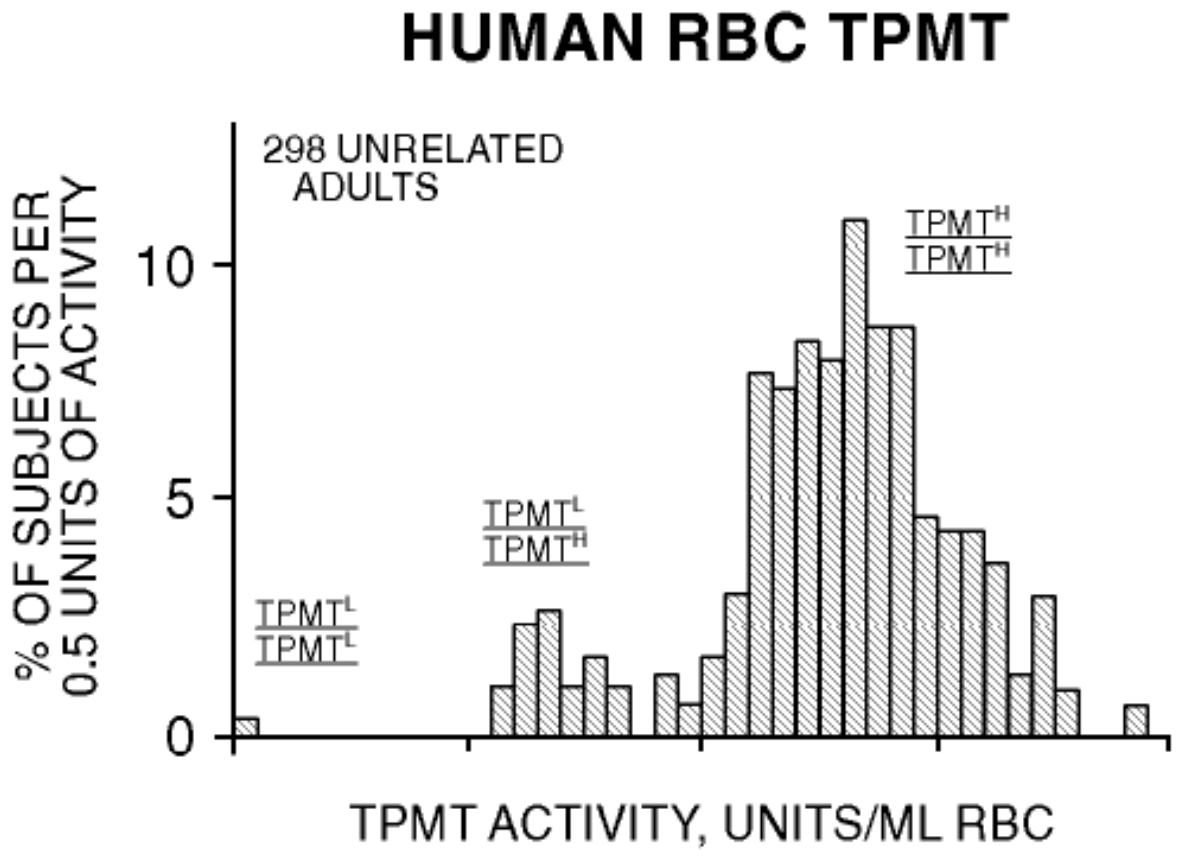
Lab: Hct 18%, Hb 6, WBC 800, Platelets 1,000: "Pancytopenia" – all blood cell levels strongly suppressed.

Role of TPMT in Metabolism of 6-thiopurine (6-TP) Medications



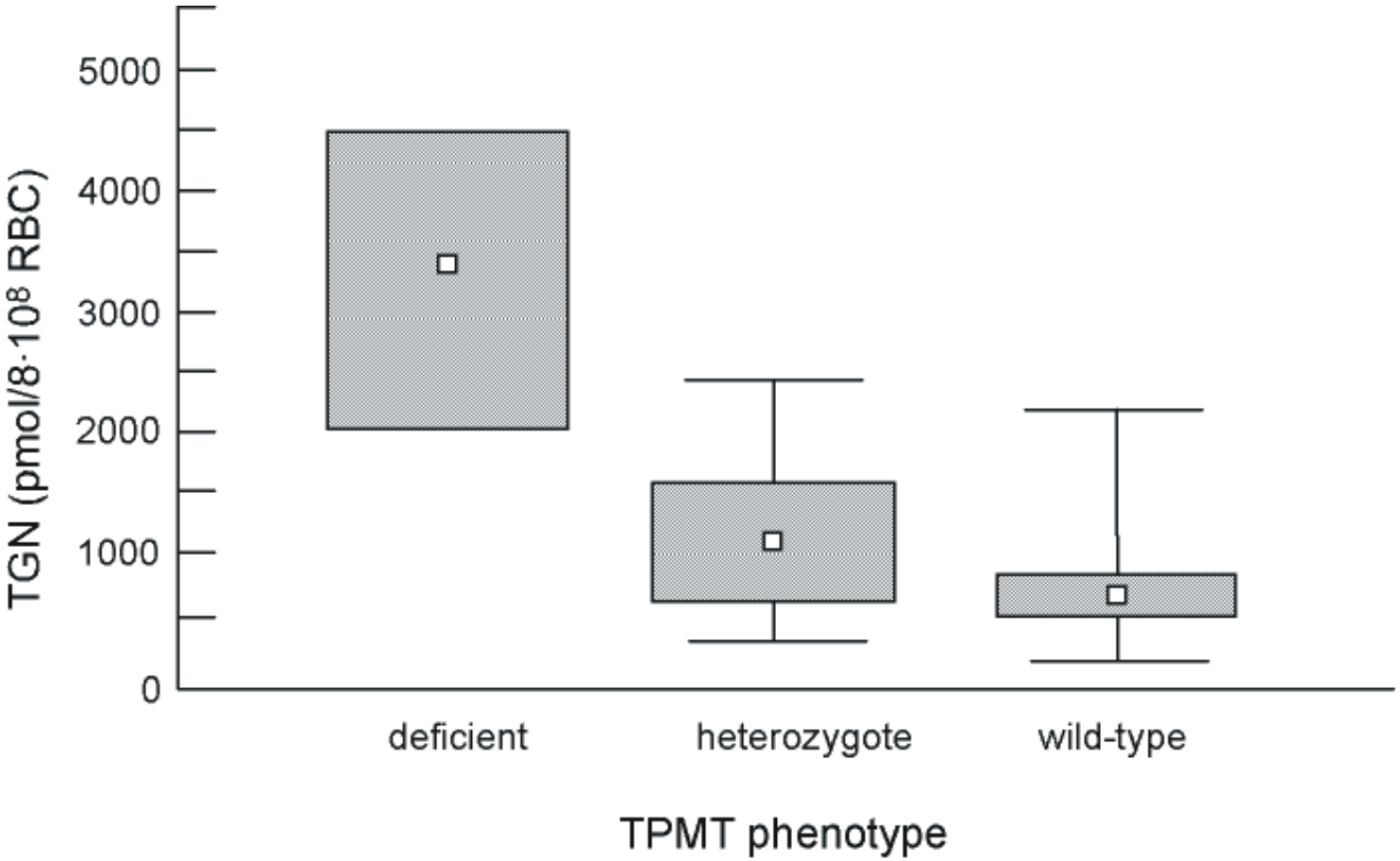
Both ***efficacy*** and ***toxicity*** are dependent on the level of 6-TGNs.

Inter-individual Heterogeneity in TPMT Activity Recognized by Weinshilboum over 20 Years Ago.



Weinshilboum and Sladek
Am J Hum Gen 32(5):651-62, 1980

Relationship between Inherited Variations in TPMT Actvity 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.nigms.nih.gov/Initiatives/PGRN
  - http://www.pharmgkb.org/

The Osmolal Gap

- Osmolality should be measured using freezing point depression (normal range: 275 – 295 mOsm/kg H_2O).
- 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 H_2O
- 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 hyperproteinemia or hypertriglyceridemia (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 H_2O}
  - 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 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 H_2O.
- Calculated serum osmolality =

  (2 * 140) + (8/2.8) + (115/18) = 289 mOsm/kg H_2O.
- Osmolal Gap = 341 – 289 = 52 mOsm/kg H_2O.
- Contribution of Ethanol to the osmolal gap

  = 146 / 4.3 = 34 mOsm/kg H_2O.
- Unexplained osmolal gap

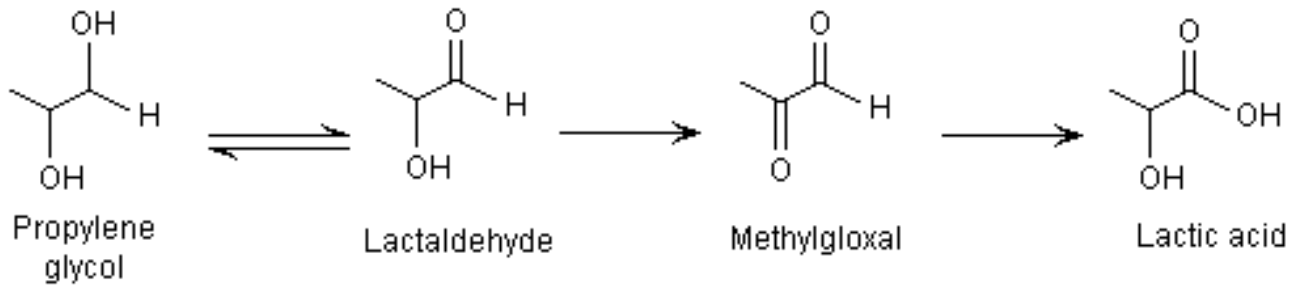
  = 52 – 34 = 18 mOsm/kg H_2O.
- What should they do?

Test for Glycols by GC

- Ethylene glycol undetected.
- Propylene glycol = 120 mg/dl (high)
- Explains Osmolal Gap of 18 mOsm/Kg H_2O:
  - 120 mg/dl / 7.1 = 17 mOsm/kg H_2O.
- Source?
  - "Pet-safe" antifreeze? – patient denies
  - 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.

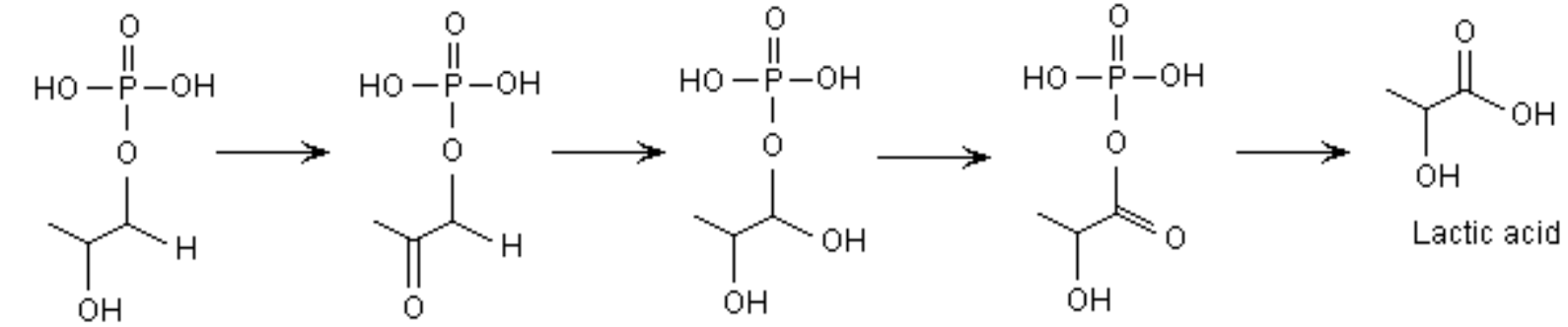
Propylene Glycol Metabolism

Pathway 1



Propylene glycol — Lactaldehyde — Methylgloxal — Lactic acid

Pathway 2



Propylene glycol phosphate — Acetyl phosphate — Lactaldehyde phosphate — Lactyl phosphate — 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 H_2O
- Calculated Osmolality (Na, BUN, Glc)

  = 299 mOsm/kg H_2O.
- Osmolal Gap

  = 326 – 299 = 27 mOsm/kg H_2O.

- 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.

Is this guy drunk or what?

- 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?

Serum Ethanol Level (mg/dL)	Effects
< 50 mg/dl	Mild muscular incoordination
50-100	Incoordination; driving increasingly dangerous
100-150	Mood, personality, behavioral changes; driving is dangerous
150-200	Prolonged reaction time; driving is very dangerous
200-300	Nausea, vomiting, diplopia, marked ataxia
300-400	Hypothermia, dysarthria, amnesia
400-700	Coma, respiratory failure, death

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-Menton mechanics with a Km < 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: [EtOH] = $\frac{49 \text{ mg/dl}}{1217}$ = **0.04%** (w/w)

Minimal metabolism:

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

124 mg/dl / 1217 = **0.10 %** (w/w)

More likely metabolism:

5 hrs***30 mg/dl/hr** = 150 mg/dl + 49 mg/dl = 199 mg/dl

199 mg/dl / 1217 = **0.16 %** (w/w)

Definitely Drunk!

Iatrogenic Intoxication

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- Became unresponsive over next ~10 hours and required intubation due to respiratory depression. Transferred to ICU.
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- Cause?
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  - (200 ml*1.04 g/ml*10^3 mg/g) / (Vd=70kg*0.58 L/kg*10 dl/L)=512 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_2O.
- Calculated osmolality: 268 mOsm/kg H_2O.
- Osmolal Gap: 315 – 268 = 47 mOsm/kg H_2O.

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:

  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:

  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 H_2O.
- 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 H_2O is accurate.
- Hence, the corrected osmolal gap is actually

  = 315 – 308 = 7 mOsm/kg H_2O.

  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)”

$$\frac{\text{mg EtOH}}{\text{dl serum}} \bullet \frac{\text{dl serum}}{\text{100 ml serum}} \bullet \frac{\text{1 ml serum}}{\sim \text{1 g serum}} \bullet \frac{\text{1 g serum}}{\text{1000 mg serum}} \bullet \frac{\text{100 \% (w/w)}}{\text{mg EtOH} / \text{mg serum}}$$

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).

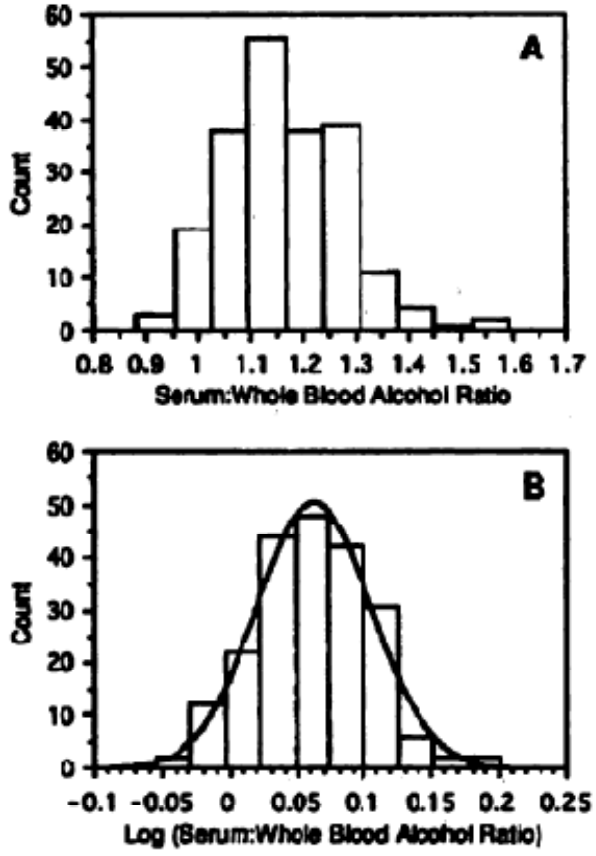

Fig. 1. Distribution histogram of serum:whole-blood alcohol concentration ratios (*A*) and the logarithmic transformation of the distribution (*B*)

The superimposed *curve* in *B* is the normal distribution, defined by the mean and SD of the data comprising the histogram

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 2. Minimum Serum Alcohol Concentrations Corresponding to Legal Intoxication at Various Probabilities

Probability	Legal standard of 0.1 g of alcohol in	
	100 mL of blood (w/v)	100 g of blood (w/w)
>50% (more likely than not)	115[a]	122
>95% (reasonable medical certainty)	140	149
>99% (beyond a reasonable doubt)	149	159

[a] 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 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