Review/Study Questions for Clinical Chemistry – Michael Hodsdon

A. Pharmacokinetics

PK #s 1-3

Multiple potential scenarios exist in which a routinely prescribed medication can result in "unexpected" toxicity, including (1) inappropriate dosing (accidental or intentional), (2) altered rates of elimination due to a change in a patient's physiology, (3) a "pharmacogenetic" variation resulting in altered drug response or metabolism, or (4) a drug-drug interaction. In each of the three clinical scenarios presented below, one of the above categories applies. Postulate/explain the most likely cause of drug toxicity in each case.

PK # 1

A 55 year old man with mild congestive heart failure has been treated successfully with digoxin for the past two years without difficulties. Intermittently measured serum digoxin levels have been within the therapeutic range (1.0 – 2.6 nM). However, recently the patient has recently suffered from a gastrointestinal virus and reports frequent vomiting and profuse watery diarrhea. Along with classic signs of depleted body water, the patient is extremely lethargic, dizzy and confused. An electrochardiogram (ECG) reveals a form of "heart block" diagnostic for digoxin toxicity. A STAT digoxin level comes back at 3.5 nM. The patient is cared for by his daughter who insists that he has been receiving the correct daily dosage of digoxin. What is the most likely explanation for the patient's recent onset of digoxin toxicity? Digoxin is ~90% bioavailable when taken orally, undergoes minimal liver metabolism and primarily eliminated by the kidneys with a half-life of 36 – 48 hours in patients with normal renal function.

Detailed Answer: This is a classic case of an altered rate of elimination due to a change in physiology. G.I. illnesses with vomiting and profuse diarrhea deplete total body water, but to a large extent this decrease is mostly in the ***extracellular*** water volume. A direct result is reduced perfusion (blood flow) to the kidneys and, hence, reduce renal function. The ability to "clear" a drug per unit time (i.e. the clearance) is decreased. This will increase the steady state level of a drug: $[drug]_{steady\ state}$ = "rate in" / Clearance. Decreasing clearance by a factor of two will increase the steady state drug level by a factor of two. However, this increase will occur slowly, over 4 – 5 half lives, which in this case is probably a total of 7 – 10 days. Therefore, we can assume that the patient has been dehydrated for many days and without appropriate hydration and/or a change in his dosage his level is likely to continue to increase.

Note that invoking a change in the patient's volume of distribution is not strictly correct. Although there can be indirect relationships between V_d and Clearance, they are not strictly related. For example, starting a 2nd medication can sometimes change the V_d of the 1st drug, without changing the clearance, usually by displacing the drug from tissue-binding sites but without competing for its metabolism or elimination. In this case, the theoretical ***steady state*** level of the drug will ***not*** change, although the "peak" values after each dose may go down. Additionally, many drugs have extremely large volumes of distribution (much larger than body water volume) due to extensive tissue binding (this is the case for digoxin). Henceforth, a change in body volume has very little effect on the drug's V_d. I gave partial credit for invoking the change in volume of distribution as it shows you are thinking along the right direction, but it isn't strictly correct.

Brief Answer: G.I. illness led to dehydration (volume depletion)
which led to decreased renal clearance of the drug
which led to increasing "steady state" drug concentrations
and after a few half-lives, patient became toxic

PK # 2

A 30 year old woman is brought to emergency room after having a seizure in the late afternoon at work. The patient is on a once daily dose of phenytoin (half life approximately 22 hours) taken in the evening (around 8 PM) with food (in order to slow absorption), which has successfully controlled her seizure disorder for the past 10 months. She reports that the previous evening she went out with friends and took her pill upon arriving at the restaurant around 7 PM. She had a couple of glasses of wine but the food was late in arriving. She rarely drinks alcohol and by 8 PM felt very "drunk" and asked to be taken home, where she promptly went to bed to "sleep it off". She felt fine in the morning and went into work. The seizure occurred later that afternoon. Detail the pharmacokinetic and pharmacologic basis for this series of events.

Detailed Answer: This scenario is a combination of "non-compliance" (not taking the drug as prescribed) and a drug-drug interaction. Since she originally took the medication on an empty stomach, contrary to her instructions (but, of course, this happens a lot in real life), she absorbed the medication much more quickly than usual. This resulted in an elevated "peak level". Note that alcohol actually speeds up the absorption of this drug, so the effect is even worsened. This will put her peak blood concentration of the drug into the toxic range, i.e. above the therapeutic range, and this is why she felt "drunk". Of course, the alcohol contributed to this feeling. Because the drug was absorbed much more quickly, there is more time for metabolism to occur, and a secondary effect is the drug will be eliminated much more quickly. This is ***not*** due to increased metabolism or increased clearance, but simply a consequence of the drug getting into her system sooner (the higher than usual peak level will also speed up metabolism overall). Hence, she had a seizure when her drug level dropped below her therapeutic range.

The point of the question was to recognize that more rapid absorption (higher peaks) can result in lower trough levels even if the dose and the rate of elimination are unaffected. It is true that alcohol induces the P450 system, which is responsible for metabolism of phenytoin. However, it is unlikely that two drinks would acutely induce expression of P450 enzymes sufficiently to cause this effect. Nevertheless, proposing P450 induction as a possible explanation does express understanding of the concepts involved and resulted in partial credit.

Brief Answer: Taking pill on empty stomach plus alcohol caused more rapid absorption
resulting in a higher peak drug level, which contributed to her drunkenness
despite an unaltered rate of elimination, the drug is metabolized quicker
leading to a lower than usual trough level the next afternoon
seizure occurs due to sub-therapeutic concentration of the drug

PK # 3

A 45 year old man is brought to the emergency room with severe pain on his right side just under his ribs. He describes having a "flu-like" illness starting a few days ago, for which he took some over the counter acetaminophen tablets. He explains that since non-prescription pain killers rarely work for him, which he associates with his superior tolerance for alcohol, he took a few "extra" pills beyond the dose recommended on the box. You estimate that he most likely ingested around 6 grams of acetaminophen per day for the past three days. This is less than the minimal toxic dose of 7.5 g for healthy adults, yet this patient does have classic signs of mild acetaminophen-induced hepatic toxicity. The patient denies having a problem with alcohol, but does routinely head down to the local pub after work with his co-workers and has 4 or 5 "drinks". On physical examination, he appears thin and poorly nourished. Explain the mechanism by which this patient might develop mild acetaminophen toxicity from an exposure that is below the accepted threshold.

Detailed Answer: This is a classic drug-drug interaction combined with a predisposing condition in the patient (malnourishment). His history of routine alcohol consumption has clearly induced his P450 system, which is responsible for converted acetaminophen into the toxic metabolite, NAPQI. This is complicated by malnourishment, which can deplete his sulfation and glucuronidation stores, reducing his ability to detoxify

NAPQI. Together, these effects will reduce his threshold for toxicity from an acetaminophen overdose because he will have more NAPQI produced and for a longer period of time from less acetaminophen than most people.

Brief Answer: Chronic alcohol consumption induced P450 enzymes in the liver

and also led to malnourishment and decreased liver sulfation/glutathione
increased P450 increased generation of toxic NAPQI metabolite
decreased sulfation/glutathione stores decreased metabolism of NAPQI
together, resulted in higher than normal [NAPQI] which caused toxicity

PK # 4

Imagine a patient who has been taking a medicine long enough to reach steady state, but is showing clinical signs of toxicity associated with an excessive drug level. This is subsequently confirmed by measurement of the drug concentration in his serum. The patient had been taking a 10 mg tablet, three times per day, which the physician recognizes is too high of a dose. The patient is told to stop taking the medication and to return each day to have his serum drug level measured. Eight days are required for his serum drug level to decrease to < 5% of his original, toxic level. At this point, the physician instructs the patient to start taking 5 mg of the same drug, three times per day (one-half the amount as before). Once again, the patient returns each day to have his serum drug level measured.

Assuming at all times that this drug has been eliminated by first-order (or linear) pharmacokinetics, how many days will be required before the patient reaches steady state and his daily serum levels will be >95% of his target (final) value? Please explain your answer.

Answer: Eight days. With 1st order pharmacokinetics, half-life determines both how long it takes for a drug to be eliminated AND how long after a new dosage is given for a patient to reach steady state. This is true regardless of the drug level or dosage. If it took eight days to fully eliminate a drug from his body (>95%), which most likely represents around 4 – 5 half lives, it will also take the same eight days for the patient to reach steady state after starting the drug again (4 – 5 half lives once again).

PK # 5

A patient presents to an Emergency Department approximately two hours after an intentional Tylenol overdose. A newly opened, but now empty, bottle of Tylenol was found at the scene, which is labeled to have originally contained twenty 500 mg acetaminophen tablets. If the patient weighs 100 kg and the volume of distribution for acetaminophen is 1 Liter per kg of body weight, estimate the patient's maximal or peak drug level (units of mg/L are fine).

Answer: Peak Drug Concentration = dose / Vd
= (20 x 500 mg) / (100 kg * 1 L/kg)
= 10,000 mg / 100 L
= 100 mg/L

PK # 6

Digoxin is used to enhance cardiac output in patients with heart failure. It has a therapeutic range of 0.5 – 2.0 ng/ml. Upon administration, digoxin has both an initial and a final volume of distribution, with a 0.5 hour equilibration half-life. The initial volume of distribution is typically one-tenth of the final volume. Dosing is based upon the final distribution volume as this is where the drug acts. For our purposes, assume that digoxin has a final volume of distribution (V_d) of 400 liters and a half-life ($t_{1/2}$) of 36 hours.

A) If a patient was being started on an intravenous infusion of digoxin, he/she would be given both an initial "loading" dose intended to reach a therapeutic level, followed by a subsequent "maintenance" dosage rate (a rate of drug infusion over time) to hold them at that steady state. Calculate the recommended loading dose and maintenance dosage (rate) for a desired therapeutic level of 1.0 ng/ml.

The loading dose is calculated using the first equation: $[drug]_{peak} = dose / V_d$

Or, rearranging loading dose = $[drug]_{peak} * V_d$

loading dose = 1.0 ng/ml * (400 L * 10^3 ml/L)

loading dose = 400,000 ng or 0.4 mg

The maintenance dose is calculated using the first equation: $[drug]_{steady\text{-}state} = rate_{in} / Cl$

Or, rearranging maintenance dose = $[drug]_{steady\text{-}state} * Cl$

maintenance dose = $[drug]_{steady\text{-}state} * [(0.693*V_d) / t_{1/2}]$

maintenance dose = 1.0 ng/ml * (0.693 * 400 L / 36 hours) * 10^3 ml/L

maintenance dose = 7,700 ng/hour or 7.7 micrograms/hour

B) Assume a scenario where the digoxin concentration in a vial has been mislabeled by the pharmacy. A patient (not previously on digoxin) is given a one-time loading dose, but because of the error the amount given is NOT known. The mistake is discovered 30 minutes (or 0.5 hrs) AFTER the (instantaneous) intravenous dose is given and a serum digoxin level measured at that time is 10 ng/ml. Despite this extremely high level, the patient does NOT show any signs or symptoms of digoxin toxicity, most likely because it is still distributing from the blood to the body. Assuming that elimination of digoxin is negligible during the distribution phase, calculate the expected final concentration in the body.

Approximately one distribution half-life (0.5 hrs) has passed since the drug was given; hence, its initial peak level (pre-distribution) was double what is now or 20 ng/ml. We also know that the final fully distributed volume is ten-fold larger than this initial volume; hence, after distribution the serum level should be one-tenth the initial peak concentration or 2.0 ng/ml.

PK #7

A hospitalized patient has been maintained on a steady-state infusion of the anti-arrhythmic drug lidocaine with a steady-state plasma level of 2 µg/mL (therapeutic range: 1.5 – 3.0 µg/mL) and an elimination half-life of 3 hours. Subsequently, the patient is started on ciprofloxaxin for treatment of a urinary tract infection, which is known to be a strong inhibitor of the enzyme (CYP1A2) responsible for metabolism of lidocaine. A few days later the patient shows signs of lidocaine toxicity and their plasma lidocaine level has increased to 6 µg/mL (at steady state). Assuming linear pharmacokinetics and no change in the lidocaine infusion rate, estimate the patient's current elimination half-life for lidocaine.

Answer: 9 hours. Simply put, everything is linear. Since there has been a three-fold increase in the steady-state level with no change in the infusion rate, then both the clearance and the elimination half-life (as they are intimately related) have also changed by three-fold. Logically, the half-life is going to be increased due to enzyme inhibition (and the clearance will decrease); hence, the new half-life is simply three times three.

PK #8

A 20 kg child is brought to the Emergency Department with a toxic lithium level of 3.0 mmol/L. Being highly water soluble, lithium is readily dialyzed and the amount removed by any single session can be determined by testing the dialysate. Assuming that the patient's current plasma lithium level is fully distributed and that the (pharmacokinetic) volume of distribution (V_d) is 0.6 L/kg ("liters" per kg of patient's body weight), calculate how much lithium in millimoles (mmol) that needs to be removed for a target level of 1.0 mmol/L after redistribution. You can assume that dialysis does ***not*** change the patient's weight or the V_d and that there is no renal

elimination during the dialysis. [Hint: start by calculating the total amount of lithium in the patient's body in millimoles.]

Answer: The total amount of lithium in the child can be calculated from the V_d and the plasma level:

[drug] = {amount of drug} / V_d

Amount of drug = [drug] * V_d

Amount of drug = 3.0 mmol/L * (0.6 L/kg * 20 kg) = 36 millimoles (mmol)

If two-thirds (24 millimoles) of this total are removed from the patient, then only one-third is left (12 millimoles) in the patient. When this 12 millimoles is distributed into the same volume (0.6 L/kg * 20 kg), the patient's new lithium level will be 12 mmol / (0.6 L/kg * 20 kg) = 1.0 mmol/L.

PK #9

Maintaining a therapeutic drug level (i.e. drug concentration within the therapeutic range) throughout an intermittent dosing interval can be challenging. Important factors to consider are the drug's half-life, rate of absorption, therapeutic index and dosing schedule. For a patient experiencing acute drug toxicity shortly after each dose (when their drug level is at its peak), but is otherwise maintaining appropriate efficacy, which of the following dosage adjustments is most appropriate (i.e. which one will best avoid peak drug levels without reducing overall efficacy).

A) Recommend taking medication on an empty stomach to increase rate of absorption.

B) Recommend taking 20 mg once per day when the patient was previously taking 10 mg twice per day.

C) Prescribe a second drug that will inhibit metabolism of the original medication.

D) Prescribe a second drug that will induce metabolism of the original medication.

E) Recommend taking medication on a full stomach to decrease rate of absorption.

Answer: (E). By decreasing the rate of absorption, peak drug levels will decrease due to ongoing metabolism of the drug during absorption. In contrast, (A) is incorrect because this will actually cause an increase in peak drug levels. Similarly, switching to a less frequent dosing interval as advised by (B) will also increase peak drug levels (note that if this answer was reversed it would be an appropriate adjustment). Lastly, changing the rate of drug elimination (answers C & D) on its own will have little effect on the peak drug levels.

B. Drug Metabolism

DM #1

Which of the following statements regarding the effect of drug metabolizing reactions are **NOT** correct.

A) Conjugation to polar highly polar molecules generally increases the water solubility of drugs.

B) Some drugs are inactive until enzymatic modification in the body, often referred to as pro-drugs.

C) The increased water solubility of drug metabolites enhances renal tubular reabsorption.

D) Drug oxidation catalyzed by phase I enzymes often reduces drug affinity for tissue-binding sites.

E) Hepatic drug metabolism can contribute to reduced oral bioavailability.

Answer: (C). Increased water solubility of drug metabolites ***reduces*** renal tubular reabsorption, thus enhancing renal excretion.

DM #2

Which of the follow drug metabolizing reactions are NOT classified as Phase II.

A) Dehydrogenation of alcohols.

B) Glucuronidation of acetaminophen.

C) Sulfation of albuterol.

D) Acetylation of sulfonamides.

E) Glutathione conjugation of chlorambucil.

Answer: (A). Dehydrogenation of alcohols (by alcohol dehydrogenase) is one of the few non-P450 Phase I reactions. It fits the definition because it involves a small chemical modification (essentially an oxidation) and not a conjugation reaction. In contrast, the other four answers are all established examples of Phase II reactions.

DM #3

Which of the following situations is likely to require a ***decrease*** in steady-state (i.e. maintenance) dosing due to altered rates of drug metabolism?

A) Barbiturate administration to a 50 year old man with advanced (non-alcoholic) liver cirrhosis and hepatic encephalopathy.

B) Barbiturate administration to a 25 year old woman with a three year history of consuming an average of five alcoholic drinks per day.

C) Warfarin administration to a 30 year old epileptic patient taking carbamazepine for chronic seizure suppression.

D) Both (A) and (C).

E) None of the above.

Answer: (A). Advanced liver cirrhosis with encephalopathy is expected to be associated with a significant loss of liver parenchyma resulting in impaired drug metabolism. A decreased barbiturate dosage would be required to maintain the same steady-state. Both chronic alcoholic consumption and carbamazepine therapy are powerful inducers of P450 metabolism, which would likely require an increased dosage of barbiturates or warfarin, respectively.

DM #4

Tamoxifen, a drug used to treat hormonally-responsive breast cancer, requires activation by the P450 system, primarily involving the enzyme CYP2D6.

A) Patients with a genetic deficiency of CYP2D6 may require either increased tamoxifen dosages or an alternative therapeutic regimen.

B) Co-administration of drugs such as cimetidine or omeprazole would be expected to enhance activation of tamoxifen.

C) Activation of tamoxifen may be expected to be reduced in elderly women.

D) Both (A) and (C)

E) All of the above.

Answer: (D). Either a selected genetic deficiency of CYP2D6 or the generic reduction in P450 activity in the elderly would reduce activation of tamoxifen, which may require an increase in dose or selection of an alternative medication that did not rely on P450-dependent activation. Both cimetidine and omeprazole are known inhibitors of P450 enzymes; hence, they would NOT be expected to enhance activation of tamoxifen.

DM #5

A 15 year old patient, with a past medical history of recurrent lymphoma and “cancer cachexia” (malnourishment), attempts suicide by ingestion of an unknown amount of acetaminophen (Tylenol) sometime within the past 24 hours. Although liver enzymes are currently elevated, their significance is unclear due to known hepatic involvement by the lymphoma. Plasma acetaminophen levels drawn at presentation and again four hours later are 120 and 80 mg/L, respectively. As a reminder, the Matthew-Rumack nomogram assumes that a “peak” acetaminophen level greater than 150 mg/L (in the U.S.) warrants treatment for potential hepatic toxicity. Which of the following clinical assessments are appropriate?

A) The malnourished state of this patient increases their risk of hepatic toxicity from any given level of acetaminophen exposure due to impairment of Phase II drug metabolism reactions.

B) Induction of the P450 system in this patient would dangerously enhance the toxicity of acetaminophen in this patient.
C) Despite the observation of decreasing plasma acetaminophen levels, both of which are below 150 mg/L, treatment with N-acetylcysteine is warranted in this patient as ingestion could have occurred up to 24 hours ago.
D) None of the above.
E) All of the above.
Answer: (E). Acetaminophen toxicity is related to a toxic metabolite ("NAPQI") produced by the P450 system. In contrast, Phase II drug metabolizing reactions are effect at "detoxifying" both acetaminophen and NAPQI. Both malnourishment, which reduces the efficacy of Phase II metabolism, and induction of the P450 system would increase the risk for toxicity. To appreciate the likelihood of hepatic toxicity in this patient, try to plot the two measured values on the Matthew-Rumack nomogram. Regardless of where you choose to "guess" at the time of ingestion, these two points suggest a "line" that will cross the toxic threshold at some point.

DM #6

In which of the following scenarios should blockade of alcohol dehydrogenase with ethanol or Fomepizole be considered.
A) Elevated osmolol gap in a patient with diabetic ketoacidosis but unequivocally negative laboratory testing for any toxic alcohol or glycol, on two separate samples collected four hours apart.
B) Any patient with a reasonable clinical suspiscion of methanol or ethylene glycol ingestion.
C) Isopropanol level of 89 mg/dL with an absence of ketosis or acidosis.
D) Both (A) and (C).
E) None of the above.
Answer: (B). Hope it was easy. In the absence of clear evidence to the contrary (answer A), blockade of alcohol dehydrogenase is warranted whenever there is a reasonable suspicion of methanol or ethylene glycol ingestion. Note that some hospitals may not have the laboratory equipment to confirm such ingestion and may require up to 72 hours before reporting a result. You should also be aware that mildly elevated osmolol gaps can be seen for many non-toxic conditions, of which DKA is most common. Lastly, isolated isoproponal ingestion is never treated with blockade of alcohol dehydrogenase as its metabolite (acetone) is much less toxic than isopropanol alone.

Advanced Overdose Case

70 kg, HIV-positive patient is on tacrolimus for immune suppression after a liver transplant many years ago. Tacrolimus is metabolized exclusively by the P450 enzyme, CYP3A4. His anti-retroviral (HIV) therapy includes ritonavir, a protease inhibitor, which is metabolized primarily by CYP3A4 and also strongly induces expression of multiple P450 enzymes. In order to maintain an average steady-state tacrolimus level of 15 ng/ml over the past few years, the patient has required a higher than usual daily oral dosage of tacrolimus of 2.0 mg (per 24 hours). The volume of distribution (V_d) for tacrolimus is 0.8 L/kg of body weight and it is 50% bioavailable. The typical half-life ($t_{1/2}$) of tacrolimus is 24 hours.

1) What is the approximate half-life of tacrolimus in this patient?

$[drug]_{steady\text{-}state} = rate_{in} / Cl$ or, rearranging $Cl = rate_{in} / [drug]_{steady\text{-}state}$

Note that we will reduce the effective daily dosage by 50% due to bioavailability.

Hence, $Cl = (0.5 * 2.0 \text{ mg} / 24 \text{ hours}) / (15 \text{ ng/ml} * 10^3 \text{ ml/L} * 10^{-6} \text{ mg/ng})$

$Cl = 2.8 \text{ L / hour}$

From above and rearranging, $t_{1/2} = (0.693 * V_d) / Cl$

$t_{1/2} = (0.693 * 70 \text{ kg} * 0.8 \text{ L/kg}) / (2.8 \text{ L/hr})$

$t_{1/2} = 13.86 \text{ hours}$

In order to enhance the efficacy of his anti-retroviral (HIV) therapy, the patient is started on a 2nd protease inhibitor, liponavir. Similar to ritonavir, liponavir is also metabolized by CYP3A4. One of the major benefits of liponavir is decreased clearance of other protease inhibitors (including ritonavir) resulting in higher steady state levels (and hence more effective viral suppression) from the same dosage of these very expensive drugs. After a month on the new protease inhibitor, our patient begins to experience unmistakable signs of tacrolimus toxicity (renal failure). His blood tacrolimus level, drawn just before his usual daily dose, is measured at 150 ng/ml (severely toxic). You can assume the patient is at steady state with regard to all medications.

2) Could a change in the bioavailability of oral tacrolimus explain the very high drug level?

If the bioavailability increased 10x due to the addition of liponavir, then it could explain a 10x increase in steady state drug level, as this is essentially a 10x increase in dosage. As tacrolimus is typically 50% bioavailable, then the most we could expect from an increase in bioavailability would be a doubling of the steady state drug level. There is a more detailed description of the effect of changing Vd on peak and trough levels at the end.

3) If liponavir decreased the volume of distribution for tacrolimus, would that explain the very high drug level?

No, changes in the volume of distribution will only affect the difference between peak and trough levels. If the clearance is unchanged, then the steady state (or "average") levels will be unchanged. If this was a "peak level" (drawn soon after a recent dose), then a 10x decrease in volume of distribution could cause this sort of increase. However, the only way for a steady state or "average" level to show this sort of increase would be due to a decrease in clearance or increase in dosage. Note: I've added an appendix that simulates the effect of a change in Vd.

4) What is the best explanation for the change in steady state levels of tacrolimus?

You were told that both tacrolimus and ritonavir were exclusively metabolized by CYP3A4. You were also told that ritonavir strongly induced multiple cytochrome P450 enzymes. When the patient was only receiving ritonavir, a higher than usual dosage of tacrolimus was required to achieve a therapeutic level, most likely due to induction of CYP3A4 and hence increased metabolism (and clearance) of tacrolimus. You were also told that the addition of liponavir reduced the clearance of ritonavir, thus necessitating lower dosages of these expensive protease inhibitors. As tacrolimus is metabolized by the same enzyme as ritonavir, it is reasonable to expect its clearance to also decrease.

Hence, the best explanation is that the addition of liponavir inhibited metabolism of tacrolimus by CYP3A4, greatly reducing the overall clearance of tacrolimus. Without a change in dosage, a decreased clearance results in a proportionate increase in steady state drug levels.

5) If the tacrolimus is abruptly stopped but the patient remains on the same dosage of both ritonavir and liponavir (for fear of inadequate HIV control), approximately how long will it take for his blood tacrolimus level to decrease from the current steady state value of 150 ng/ml to below 40 ng/ml? You can assume that clearance of tacrolimus remains first order. You can also assume that neither the bioavailability nor the volume of distributrion of tacrolimus was affected by the addition of liponavir.

Correct answer is 280 hours. Since his steady state level has increased tenfold without a change in dosage, then his clearance must have had a "linear" change as well. As the volume of distribution is also unchanged, the half-life will also respond linearly. Hence, his new half-life is 10 x 14 hours or 140 hours. This means that it will take him 140 hours to go from 150 to 75 ng/ml, another 140 hours to go from 75 to 37.5 ng/ml, or a total of approximately 280 hours (two half-lives) to drop below 40 ng/ml.

Clearly, we cannot wait 280 hours for the tacrolimus to clear on its own, due to ongoing renal toxicity. Oftentimes, we would consider accelerating the drug clearance artificially by hemodialysis, hemoperfusion, or plasmapheresis. However, as >90% of tacrolimus is intracellular (in blood, this means that it is all essentially in RBCs; we use a whole blood cell lysate for measuring total levels), none of these options will work.

6) We might consider reducing the level using red cell exchange (basically, remove a bunch of the patient's whole blood and replace with units of packed RBCs, saline and plasma). How much would a single exchange transfusion lower the patient's tacrolimus blood level, if it was measured after all the tacrolimus in the body was allowed to fully redistribute? You should assume that the patient's blood volume is 5 L and that a single exchange transfusion replaces ~2/3 of the patient's whole blood, which has an initial tacrolimus level of 150 ng/mL. You can also assume that the exchange is rapid relative to redistribution.

First we estimate how much tacrolimus is in the patient's body before the exchange transfusion using the volume of distribution ([drug]*Vd = total drug in body): 70 kg * 0.8 L/kg * 150 ng/mL * 1000 mL/L = 8,400,000 ng (or 8.4 mg).
The amount of tacrolimus in the patient's blood volume is 150 ng/mL * 5000 mL = 750,000 ng (or 0.75 mg) and 2/3 of this would be removed by a single exchange transfusion, or 2/3 * 750,000 ng = 500,000 ng (or 0.5 mg). After the exchange transfusion, there will be 8.4 – 0.5 = 7.4 mg of tacrolimus in the patient's body, which will distribute into the same 70 kg * 0.8 L/kg = 56 L. Hence, the new blood level will be 7.4 mg/56 L = 0.132 mg/L = 132 ng/mL. This is a rather small decrease in the level. Many exchange transfusions would be required to reduce the patient's level to a non-toxic level, each requiring exposing the patient to six units of RBCs, along with other potential side effects of the procedure (viral infection, alloantibody formation, transfusion reaction, infection, iron overload, coagulopathy, etc.).

Note that intermittent (e.g. daily) exchange transfusions work like a 1st-order process as they eliminate a constant fraction of drug per procedure, in this case (two-thirds of 5 L / 56 L) ~ 6% every 24 hours.

7) What should they do?

Take the patient off of liponavir and temporarily provide an alternative protease inhibitor that does NOT strongly inhibit CYP3A4 (and preferably that induces it). When this was done in this case, the tacrolimus level quickly decreased to 15 ng/mL (therapeutic) in a few days. Once the liponavir cleared, CYP3A4 remained induced and the effective half-life quickly returned to ~ 14 hours.

8) Assuming that the patient must remain on the ritonavir/liponavir combination for optimal HIV suppression, what is the best choice of initial dosage?

We know that at steady state this patient will clear tacrolimus at 0.28 L/hr (simply 1/10 the original clearance calculated for question #1). If we want a steady state level of 15 ng/mL, then the patient must be dosed at 15 ng/mL * 0.28 L/hr * 1000 mL/L = 4,200 ng/hr * 24 hrs/day * 10^{-6} mg/ng = 0.1 mg/day. Since it is given P.O. and only 50% bioavailable, dosage is actually 0.2 mg/day. Or, since everything is linear, 1/10 the original dose of 2.0 mg/day.

Appendix: Extra Info on Question #2.

There is a rather complicated discussion about the effect of changing Volume of Distribution on drug levels. I have run some simulations in MATLAB and am sharing the results. A figure is below. The green line(s) represent the initial conditions for the patient with a Vd = 56 L, a Cl = 2.8 L/hr, on a dose of 2 mg every 24 hours, and assuming a 50% bioavailability. The Y-axis gives the plasma drug concentration in ng/mL and the X-axis represents time given in days (not hours).

There are two green lines, one is for intermittent oral dosing, and the other is for a "matched" steady state infusion. You can see that the average or steady-state infusion concentration is 15 ng/mL as given in class (which we assumed was the steady-state value; the true trough is a little lower). By the way, I also assumed a 3 hour half-life for absorption. This is why the curves are not directly vertical after each dose.

The red and blue curves are exactly the same as the green, except that I lowered the Vd by 1/2 for the red lines and 1/10 for the blue. You can see how the infusion lines overlap after steady state is reached, which is expected as we did not change Clearance, only Vd. However, for intermittent dosing there is a large change in the peak levels after each dose and a smaller reduction in trough values. Note that the "average" concentration stays about the same, albeit with much larger fluctuations.