

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 electrocardiogram (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.

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.

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.

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.

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).

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.

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.

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 $\mu\text{g/mL}$ (therapeutic range: 1.5 – 3.0 $\mu\text{g/mL}$) and an elimination half-life of 3 hours. Subsequently, the patient is started on ciprofloxacin 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 $\mu\text{g/mL}$ (at steady state). Assuming linear pharmacokinetics and no change in the lidocaine infusion rate, estimate the patient's current elimination half-life for lidocaine.

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.]

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.

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.

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.

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.

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.

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.

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 suspicion 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.

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?

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?

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

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

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 distribution of tacrolimus was affected by the addition of liponavir.

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 $\sim 2/3$ 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.

7) What should they do?

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