**2006-7, Pharmacology 504B, *Interfering Selectively* Final Examination Questions**

In class, we discussed multiple potential scenarios 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. Choose ***two*** of the three cases and postulate/explain the most likely cause of drug toxicity in each case.

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 2$^{nd}$ medication can sometimes change the $V_d$ of the 1$^{st}$ 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

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

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

# Fall 2007 Exam

**Question 1, Part A:**

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.

**Question 1, Part B:**

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).

**Question 2:**

For most pharmaceuticals, serum (or plasma, or whole blood) is the preferred sample for measuring drug levels in order to guide therapy (and check for toxicity). However, most drugs (or their metabolites) can also be found in urine, yet urine is virtually never used for therapeutic drug monitoring. In contrast, urine can be very useful for drugs of abuse testing, where the tester is interested in high sensitivity for any recent drug use. Please explain why serum is preferred for therapeutic drug monitoring and urine is preferred for drugs of abuse testing.

**Answer to Question 1, Part A:**

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).

**Answer to Question 1, Part B:**

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

**Answer to Question 2:**

Serum drug levels are generally in equilibrium with tissue sites of action and, therefore, correlate well with the current efficacy and/or toxicity of the medication. On the other hand, urine generally contains long lived, inactive drug metabolites, which persist well after the clinical effect is gone. Note that this is desirable for drugs of abuse testing because the goal is to be sensitive for any past use. Another reason why urine is not good for therapeutic drug monitoring is that drug concentrations will vary based upon the hydration status of the patient. A dehydrated person makes very concentrated urine and drug concentrations will be very high and, as I am sure all of you are aware, if you drink a large amount of water (or even better caffeinated soda), your urine will be very dilute. This makes it nearly impossible to correlate urine drug concentrations with serum drug levels.

# Fall 2008 Exam

1. A 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 liponavir, 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 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.

A) Calculate the effective half-life of tacrolimus in this patient [don't forget that $Cl = (0.693*V_d)/t_{1/2}$].

$[drug]_{steady\text{-}state} = rate_{in} / Cl$ 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, $t_{1/2} = (0.693 * V_d) / Cl$

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

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

B) How does this compare to the normal half-life of tacrolimus? Why is it different?

The half-life of tacrolimus has been greatly reduced in this patient compared to normal. This is a result of overall induction of the P450 enzyme, CYP3A4. Even though liponavir is metabolized by CYP3A4, and thus potentially inhibitory, its net effect must be induction of CYP3A4. Higher levels of CYP3A4 increased the enzymatic clearance of tacrolimus, with a corresponding decrease in the effective half-life.

In order to enhance the efficacy of his anti-retroviral (HIV) therapy, the patient is started on a 2nd protease inhibitor, ritonavir. Similar to liponavir, ritonavir is also metabolized by CYP3A4. One of the major benefits of ritonavir is decreased clearance of other protease inhibitors (including liponavir) 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. His blood tacrolimus level is measured at 150 ng/ml. Repeated daily levels confirm that this is a steady-state level. However, his tacrolimus dosage has not changed.

C) Given what you have been told about the effect of ritonavir on liponavir clearance, postulate a mechanism for the dramatically increased steady state levels of tacrolimus in this patient. What is his new half-life for tacrolimus?

Ritonavir must be a net, powerful inhibitor of CYP3A4, which is the only explanation for its benefit of decreased clearance of other protease inhibitors metabolized by the same enzyme. This inhibition of CYP3A4 will similarly decrease the clearance of tacrolimus. Without a change in dosage, the net effect on tacrolimus levels will be a steady increase in drug levels until a new steady state is achieved. Since his new steady state is ten-fold greater than before, with the same dosage of medication, then we know his clearance has decreased ten-fold. Half-life is inversely proportional to clearance; hence, his half-life will have increased ten-fold to 138.6 hours or about 5 days.

D) If both the ritonavir and the tacrolimus are abruptly stopped and assuming that the enzyme levels CYP3A4 are the same as before the ritonavir was started (i.e. in part "A", above), how long will it take for his blood tacrolimus level to decrease below 20 ng/ml? You can assume that the ritonavir is cleared instaneously from the body after it is stopped.

After removal of the ritonavir, the half-life of tacrolimus should be the same as was calculated in "A", above, or ~14 hours. Hence, he will decrease from 150 to 75 to 37.5 to 18.75 in approximately three half-lives or 42 hours.

2. 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.

# Fall 2009 Exam

**Question 1**

A 70 kg patient is being started on an intravenous infusion of lidocaine for control of a ventricular arrhythmia. A steady state plasma concentration of 1 mg/L is desired. Using a volume of distribution of 0.1 L/kg (of body weight) and a half-life of 2 hours, calculate an appropriate ***initial loading dose*** (or bolus) to quickly reach 1 mg/L and also calculate an appropriate maintenance dose to maintain a steady state level of 1 mg/L (5 points total).

Loading dose calculation: $[drug]_{peak} = dose / V_d$

or $loading\ dose = [drug]_{peak} * V_d$

$loading\ dose = 1\ mg/L * 0.1\ L/kg * 70\ kg$

$loading\ dose = 7\ mg$

Maintenance dose calculation: $[drug]_{steady\ state} = rate_{in} / Cl$

or $rate_{in} = [drug]_{steady\ state} * Cl$

But need to calculate Cl first: $Cl = 0.693 * V_d / t_{1/2}$

$Cl = 0.693 * 0.1\ L/kg * 70\ kg / 2\ hrs$

$Cl = 2.4\ L/hr$

$rate_{in} = 1\ mg/L * 2.4\ L/hr$

$rate_{in} = 2.4\ mg/hr$

The patient is put on cardiopulmonary bypass (their bloodstream bypasses the heart and is mechanically pumped outside the body), which is known to causes the volume of distribution for lidocaine to double (2x) without changing its clearance. What is the effect of this isolated change in volume of distribution on the elimination half-life and the steady state drug level of lidocaine in this patient (5 points total)?

If the volume of distribution goes increases but the clearance stays the same, then the elimination half-life has to increase proportionately; i.e. it will become 4 hours. This is evident in the equation: $Cl = 0.693 * V_d / t_{1/2}$. However, the steady state drug concentration depends only on the $rate_{in}$ and Cl, which is also demonstrated in the equation $[drug]_{steady\ state} = rate_{in} / Cl$. Hence, despite the increase in $V_d$ and the $t_{1/2}$, the steady state drug concentration remains the same (1 mg/L).

**Question 2**

Amonafide is an investigational agent being studied in early clinical trials. The dose limiting toxicity of amonafide is bone marrow suppression (with correspondingly low blood cell counts). Amonafide is metabolized to N-acetylamonafide. Is this an example of Phase I or Phase II drug metabolism (2 point)?

Phase II metabolism, which involves conjugation or addition of small, polar molecules to a drug and includes glucuronidation, acetylation, sulfation, amongst other reactions.

A study followed blood levels of amonafide and N-acetylamonafide in patients maintained on similar doses of amonafide. The ratio of blood N-acetylamonafide to amonafide concentration was compared to white blood cell count for each patient. At steady state, approximately half of the patients demonstrated high ratios of N-acetylamonafide to amonafide (> 5:1) and low blood cell counts, while the other half of the patients exhibited very low ratios (< 1:5) and normal blood cell counts; whereas, the beneficial effect of the drug (efficacy) was the same in both groups. From this information, postulate whether amonafide or its metabolite, N-acetylamonafide, is primarily responsible for the bone marrow suppression (2 point).

N-acetylamonafide is clearly responsible for the toxicity as only the patients with high levels (compared to amonafide) developed low blood cell counts.

What is the most likely explanation for the variability in N-acetylamonafide to amonafide blood levels at steady state (2 point)?

This is most likely a pharmacogenetic issue. The acetylating enzyme is likely genetically deficient in the people with high ratios. NAT1 is a known polymorphic acetylating enzyme and would be a candidate, though others are also possible.

If N-acetylamonafide could be independently synthesized, it might be considered as an alternative to amonafide. Are the following potential advantages and disadvantages true or false (1 point each)?

1) There would be no need for pre-establishing pharmacogenetic status before administering N-acetylamonafide as all people would respond the same and thus could be dosed similarly.
2) In patients taking a P450 inhibitor, amonafide would be a safer choice because it wouldn't be as readily converted into N-acetylamonafide.
3) N-acetylamonafide would be less readily absorbed than amonafide requiring higher doses to achieve the same effect.
4) N-acetylamonafide is likely to have a longer half-life than amonafide requiring less medication to maintain steady state.

1) True; 2) False; 3) True; 4) False

# Fall 2010 Exam

**Question 1, Part 1 (2 points)**
Imagine a drug that is eliminated entirely by glomerular filtration, but 50% of the filtered drug is reabsorbed back in the proximal tubule and returns to the system circulation. The other 50% of the filtered drug is excreted into the urine. In a person with a glomerular filtration rate of 100 mL/min (same as 6 L/hr), ***what would you calculate is their drug clearance*** (choose whichever units you want, just be sure to specify)? You can assume that 100% of the drug is free in circulation.

This is easy, but can be tricky to get right. The answer is simply 0.5 * 6 L/hr = 3 L/hr. Think how much is excreted in one hour. During that hour, 6 Liters of blood was filtered of all the drug it contained, but half was returned to the circulation and the other half excreted from the body. Hence, the person excreted the same amount of drug contained by 3 Liters of blood.

**Question 1, Part 2 (2 points)**
You follow the elimination of the drug from this person's body and calculate a $t_{1/2}$ (half-life) of 10 hrs. Using whatever you calculated for the clearance in Part 1 (even if you did it wrong), calculate their predicted volume of distribution ($V_d$).

Remember the equation: $t_{1/2} = 0.693 * V_d / Cl$. This can be rearranged as $V_d = (t_{1/2} * Cl) / 0.693$.
Hence $V_d$ = (10 hrs * 3 L/hr) / 0.693 = 43.3 Liters.

**Question 1, Part 3 (2 points)**
Calculate the half-life for a patient that weighs 50% more (1.5x) than the patient with a 10 hour half-life. You can assume that clearance is unchanged by weight and that the $V_d$ for this drug is directly proportional to weight.

From the above equation, it should be obvious that the half-life will also be 50% longer, or 15 hours:
$t_{1/2} = 0.693 * V_d / Cl$. So, $t_{1/2}$ = 0.693 * 1.5 * 43.3 (L) / 3 (L/hr) = 15 hrs.

**Question 1, Part 4 (2 points)**
Calculate the loading dose required to bring the heavier patient up to a peak level of 10 µg/L.

$[drug]_{peak} = dose / V_d$; or $dose = [drug]_{peak} * V_d$
dose = 10 µg/L * 64.95 L = 649.5 µg or 0.65 mg

**Question 1, Part 5 (2 points)**
Calculate the maintenance dose required to hold the person at 10 µg/L during a continuous infusion.

$[drug]_{steady\text{-}state} = rate_{in} / Cl$; or $rate_{in} = [drug]_{steady\text{-}state} * Cl$
$rate_{in}$ = 10 µg/L * 3 L/hr = 30 µg/hr

Question 2
Oxycodone is a powerful analgesic (pain reliever). It is metabolized in the liver by a cytochrome P450 enzyme to Oxymorphone. At the same time, both oxycodone and oxymorphone are conjugated with glucuronic acid, at the same rate, and excreted into the urine. Both the free forms of oxycodone are oxymorphone are ***equally*** effective pain

relievers, but the glucuronidated forms of both have NO physiologic effect. For the five scenarios below, tell me if the patient requires a higher, lower or the same dose ***to achieve the same analgesic effect*** as a healthy, non-medicated person who doesn't drink alcohol. In each case explain your reasoning. (2 points each)

1) A cancer patient that is functionally malnourished due to "cancer cachexia"?

Lower dose because of decreased glucuronidation (Phase 2 metabolism), which converts the active forms of the drug to its inactive forms.

2) A patient taking carbamazepine.

No change. Carbamazepine induces P450 enzymes, which in this case will increase the conversion of oxycodone to oxymorphone. However, as both of these are active and both are glucuronidated at the same rate, no dosage adjustment is needed.

3) A very ***mal***nourished chronic alcoholic?

Lower dose. This one is a little tricky. This is a combination of the first two scenarios. Their P450 enzymes will be induced, but that won't require dosage adjustment. However, they will also be deficient in glucuronic acid due to malnourishment. So, the conversion of active to inactive will be slowed and a lower dose is required.

4) A patient on high dose cimetidine.

No change. Cimetidine inhibits P450 enzymes, which will decrease the conversion of one active form to another. The total amount of oxycodone and oxymorphone will stay the same, only the relative amounts of each will change. And the overall rate of glucuronidation will stay the same.

5) A patient with kidney disease (glomerular filtration rate approximately ¼ of normal) but normal liver function.

No change. Only hepatic metabolism matters. The circulating concentrations of the two glucuronidated forms will increase due to the decreased renal function, but they are inactive. Conversion of active to inactive will stay the same.