1. A 100 kg patient is to be treated p.o. with sodium phenytoin capsules. Assuming a phenytoin volume of distribution of 0.7 L/kg, Km of 4 mg/L and Vmax of 7 mg/kg/day, calculate the following:
   a. The loading dose to produce an initial concentration of 18 mg/L. How would you administer this dose?
   b. The daily maintenance dose to produce an average steady state concentration of 15 mg/L.

   \[ V_d = 70 \text{ L} \]

   sodium phenytoin is 92% phenytoin

   \[ LD = \frac{18 \cdot 70}{0.92} = 1370 \text{mg} \rightarrow 1400 \text{mg} \quad (500-500-400 \text{ every 2 hours}) \]

   \[ MD = \frac{7 \cdot 100 \cdot 15}{(4+15) \cdot 0.92} = 600 \text{mg/day} \]
2. M.K., a 58-year-old, 60 kg female, was admitted to the hospital in status asthmaticus. She received an IV aminophylline loading dose of 375 mg at 9 p.m., followed by a constant aminophylline infusion of 60 mg/hr. The next morning at 7 a.m. (ten hours after the bolus and initiation of the infusion) a plasma sample was obtained and the reported theophylline concentration was 18 mg/L. Calculate the apparent clearance and half-life of theophylline in M.K. Assuming that the desired steady-state plasma theophylline concentration for M.K. is <20 mg/L, determine whether the maintenance dose needs to be adjusted.

\[
C_0 = \frac{0.85 \cdot 375}{30} = 10.6 \mu g/mL
\]

\[
CL = \frac{2 \cdot 60 \cdot 0.85}{(10.6+18)} + \frac{2.30 \cdot (10.6-18)}{(10.6+18) \cdot (10-0)} = 3.567 - 1.552 = 2.01 L/h
\]

\[
t_{1/2} = \frac{0.693 \cdot 30}{2.01} = 10.3 h
\]

\[
C_{ss} = \frac{60 \cdot 0.85}{2.01} = 25.4 \mu g/mL \rightarrow \text{too high}
\]

decrease infusion rate to 45 mg/h \(\rightarrow C_{ss} = 19 \mu g/ml\)

3. A patient (35 years old, 65 kg) is to be started on intravenous phenobarbital sodium. The therapeutic range is 10-30 mg/L. A loading dose is given so as to yield a \(C_{p0}\) of 30 mg/L. Calculate this loading dose and the daily maintenance dose to produce an average steady state concentration of 20 mg/L.

\[
V_d = 0.65 L/kg = 42.3 L
\]

\[
CL = 0.004 L/h/kg
\]

\[
LD = \frac{42.3 \cdot 30}{0.9} = 1410 mg \rightarrow 1.5 g
\]

\[
MD = \frac{0.004 \cdot 24 \cdot 65 \cdot 20}{0.9} = 139 mg/day \rightarrow 150 mg/day
\]
4. GB is a 56 yo renal transplant recipient stabilized on oral tacrolimus as his immunosuppressant. He is also taking 100 mg ketoconazole per day to decrease tacrolimus cost and to provide the antimicrobial benefits of the ketoconazole. GB is admitted to the hospital and is put on IV tacrolimus with the dose determined by assuming a bioavailability. Discuss the potential problems with this and what you would expect to happen to GB’s tacrolimus concentrations.

There are several potential problems here. First is the assumption of a bioavailability. While it may be necessary to make such an assumption, there is a good chance that your assumption will be wrong. The reason is that tacrolimus and cyclosporine have large interpatient variability in F, due largely to the wide interpatient variability in expression of intestinal CYP3A4 and P-gp. The other problem is that with oral dosing, keto will be inhibiting gut 3A4 and/or P-gp (thus increasing tacro F) and inhibiting hepatic 3A4. When given IV, the only inhibition with keto will be in the hepatic metabolism. Thus, if conversions to IV are based on the inhibited po dose, it is likely that concentrations will fall out of the therapeutic range with the IV dosing (e.g. an example I gave in class: ketoconazole increased cyclosporine F by 155% and decreased CL by only 45%). Must understand that keto is inhibiting things in the gut and the liver, thus will cause greater inhibition of oral dosing as compared to IV dosing.
5. PT is a patient stabilized on chronic phenytoin therapy. She has just been diagnosed with rheumatoid arthritis and her physician would like to start her on high dose aspirin therapy. However, the physician is concerned about a possible drug interaction with aspirin. You find in your pocket reference that high dose aspirin is known to displace phenytoin from its plasma protein binding sites. Describe (as you would to the physician) the clinical relevance of this interaction and your therapeutic recommendations.

While it is true that aspirin displaces phenytoin from its plasma protein binding sites, there is no reason to alter the phenytoin dose or switch from aspirin to another agent just because of the drug interaction. Specifically, phenytoin is a low extraction, restrictively cleared drug. This means that it’s clearance is determined by unbound clearance and fraction unbound. Addition of aspirin to the regimen will lead to an increased unbound fraction of phenytoin. This will increase phenytoin’s clearance and decrease it’s total drug concentration. HOWEVER, unbound concentration will be unchanged as it is determined only by dose and unbound clearance. Therefore the free (and pharmacologically active) phenytoin concentration will be unchanged in spite of this drug interaction, thus changes in dosage will be unnecessary. However, it is important for the physician to understand that the total phenytoin concentration will decrease, in spite of no change in the free concentration. For example, if phenytoin free fraction increases from 10% to 15% the following total concentration will change as follows:

\[
\text{Total Cp} = \frac{\text{Unbound Cp}}{\text{fu}}.
\]

Remember unbound Cp doesn’t change in this interaction because unbound clearance doesn’t change. Therefore the following will be seen:

Before aspirin: 
- total Cp – 12 mcg/ml
- fu – 0.10
- unbound Cp – 1.2 mcg/ml

After aspirin: 
- total Cp – 8 mcg/ml
- fu – 0.15
- unbound Cp – 1.2 mcg/ml

If the medical team is unaware of this, and measures a total phenytoin level, the normal reaction would be to increase the dose, which would be inappropriate and likely to lead to toxicity.

6. Explain why the volume of distribution for antipyrine goes down in the elderly (0.47 vs. 0.58 L/kg), whereas that for diazepam goes up (1.7 vs. 2.6 L/kg)

Antipyrine distributes in total body water → less in the elderly
Diazepam distributes into body fat → more in the elderly