1. Which combination of the following pharmacokinetic changes is the best one to describe the elderly and neonates? (These groups share similar PK characteristics.) (1 point)

1). Low renal clearance
2). Relatively less body water
3). Low metabolic clearance
4). Decreased protein binding
5). Longer half-lives

A) 1 & 4
B) 1, 3, & 4
C) 1, 3, 4 & 5
D) 1, 4, & 5
E) all of the above

Answer: C
2. 50 year old, 70 kg male has been receiving 200mg/day (100 mg BID) of phenobarbital (S=1) for the past 25 days. Please calculate the phenobarbital plasma concentration just before the morning dose on Day 26. (2 points)

For phenobarbital $V_d = 0.7 \text{ L/kg}$, $CL = 0.004 \text{L/h/kg}$ for adults

$Cl = 0.004 \text{L}/\text{h/kg} \times 70 \text{kg} = 0.28 \text{L/h}$

$V_d = 0.7 \times 70 = 49 \text{ L}$

$k_e = \frac{CL}{V_d} = \frac{0.28 \text{L/h}}{49 \text{L}} = 0.00571 \text{h}^{-1} = 0.137 \text{day}^{-1}$

$t_{1/2} = 0.693 / 0.137 = 5.05 \text{ day}$, so after 25 days (about 5 half-life), the steady state should be achieved.

$\tau = 12 \text{h} = 0.5 \text{ day}$

$$Cp_{ss\text{min}} = \frac{D \cdot S \cdot F \cdot e^{-ke\tau}}{V_d \cdot (1 - e^{-ke\tau})} = \frac{100 \text{mg} \cdot 1 \cdot 1 \cdot e^{-0.137 \cdot 0.5}}{49 \text{L} \cdot (1 - e^{-0.137 \cdot 0.5})} = 28.78 \text{mg/L}$$
3. 42 year old, 62.5 kg female will receive carbamazepine regimen, please calculate a daily oral dose to achieve average steady plasma concentration of 7mg/L for monotherapy (Please use the key parameters available in the slides). (1 point)

Carbamazepine is an anticonvulsant agent, its clearance = 0.064 L/h/kg for monotherapy (Monotherapy represents the patient does not receive other enzyme-inducing anticonvulsants, e.g. Phenobarbital, phenytoin.).

\[
\text{Daily Dose} = \frac{Cl \cdot C_{ppss} \cdot \tau}{S \cdot F} = \frac{(0.064L/h/kg) \cdot 62.5kg \cdot (7mg/L) \cdot 24h}{1 \cdot 0.8} = 840mg \text{ for IR (F=0.8) and 960 mg for XR (F=0.7)}
\]

Note: You can also round the dose reasonably.
4. H.T., a 52 year-old, 68 kg male, had been taking 300 mg/day of sodium phenytoin. However, his seizure was poorly controlled and his plasma concentration of the drug was only 7 mg/L. So his dose was increased to 400 mg/day. Then he began to complain about minor CNS side effects and his reported phenytoin plasma concentration is 22 mg/L. His renal and hepatic function is normal. It is assumed that both of the reported plasma concentrations represent steady-state levels and that H.T. has complied with the prescribed dosing regimens.

Calculate H.T.’s apparent Vm and Km and a new daily dose of phenytoin that will result in a steady-state level of about 15 mg/L. (3 points)

\[
V_{\text{max}} = \frac{D_1 \cdot D_2 \cdot (C_2 - C_1)}{C_2 \cdot (D_1 - C_1 \cdot D_2)} = \frac{300 \cdot 400 \cdot (22 - 7)}{22 \cdot 300 - 7 \cdot 400} \approx 474 \text{ mg} \quad \text{(sodium phenytoin)}
\]

\[
K_M = \frac{C \cdot (V_{\text{max}} - D)}{D} = \frac{22 \cdot (474 - 400)}{400} = 4.07 \text{ mg/L} \quad \text{(phenytoin)}
\]

New daily dose: \[
D = \frac{V_{\text{max}} \times C}{K_M + C} = \frac{474 \times 15}{4.07 + 15} \approx 373 \text{ mg sodium phenytoin which can be rounded to 380 mg (sodium phenytoin).}
\]

Note:

Although \( F = 1 \), \( S=0.92 \) for sodium phenytoin, here what the \( V_{\text{max}} \) get is sodium phenytoin, so for the equation to calculate a new daily dose \( D \), it doesn’t need a salt factor (S) to do the calculation.
5. N.J., a 48 year old 70 kg intermittent asthmatic patient, presents to the emergency room with severe dyspnea, coughing, and wheezing. He was treated there with aerosol albuterol, but was only partially relieved. He was then given 400 mg of IV aminophylline (dihydrate salt form) over 30 minutes. Thirty minutes after the loading dose was administered (1 hr from time zero) his theophylline concentration was 15µg/ml. After the loading dose, he was started with an aminophylline IV constant infusion of 55 mg/hr. His serum theophylline level was measured as 9µg/ml after eight hours from the first measured serum level (9 hr from time zero). He smokes 1 pack of cigarettes a day and has normal liver, kidney, and heart function and is afebrile. (Vd = 0.5L/kg)

1). Calculate the total body clearance. (1 point) 
2). Calculate the additional IV aminophylline loading dose necessary to increase his level from 9µg/ml back to 15µg/ml. (1 point) 
3). Calculate N.J.’s expected steady state theophylline concentration for the infusion rate of 100mg/h aminophylline. (1 point) 

For aminophylline anhydrous: F=0.85; aminophylline dihydrate: F=0.80

Here, F = 1, S=0.8 (A)

Vd = 0.5L/kg *70kg = 35L

1). Using Chiou equation for constant IV infusion

\[
CL = \frac{2 \cdot k_0 \cdot F \cdot S}{(C_1 + C_2) + 2 \cdot Vd \cdot (C_1 - C_2) \cdot (t_2 - t_1)} = \frac{2 \cdot 55\text{mg/h} \cdot 1 \cdot 0.8}{(15 + 9)\text{mg/L}} + \frac{2 \cdot 35L \cdot (15 - 9)\text{mg/L}}{(15 + 9)\text{mg/L} \cdot 8h} = 3.67 + 2.19 = 5.86L/h
\]

2). \[LD = \frac{\Delta Cp \cdot Vd}{S \cdot F} = \frac{(15 - 9)\text{mg/L} \cdot 35L}{0.8 \cdot 1} \approx 263mg\]

3). \[Cp_{ss} = \frac{k_0 \cdot S \cdot F}{CL} = \frac{100\text{mg/h} \cdot 0.8 \cdot 1}{5.86L/h} \approx 13.65\text{mg/L}\]

Note:
Clearance-Factor (smoking 1.6) is used to do the estimation from population average. Here there are measured data which can be used to calculate the clearance, so it doesn’t need a clearance factor to do the calculation.