Question 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) 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, 4, &5  
D) 1, 3, 4 &5  
E) all of the above

Answer: D
Question 2

A clinical study was conducted to assess the effect of carbamazepine on the pharmacokinetics of drug X after a single oral dose. The mean drug X concentration-time profile is shown in the Figure. It is known that drug X is metabolized mainly by CYP3A4. Describe the graph and make a conclusion.

Answer

1) The peak plasma concentrations and AUC of Drug X administered alone are higher than that with carbamazepine co-administration.

2) Carbamazepine is a potent inducer of CYP3A4 which influenced the concentrations of Drug X significantly.
Question 3

D.W., a 60-year old, 74 kg male, alcoholic, epileptic patient, has been taking phenobarbital (200 mg daily at bedtime) for three years. He has been free of seizures for at least one year. He was admitted to the hospital on January 10 with ataxia and general central nervous system depression, without alcohol on his breath. A plasma phenobarbital concentration of 56 mg/L was measured in a blood sample drawn at 10:00pm of that day. The drug was discontinued (including no dose on January 10) and another blood sample was obtained on January 16 at 10:00pm to determine if the patient was metabolizing the drug more slowly than expected, as the patient had signs of hepatic cirrhosis. The second concentration was 16 mg/L.

a. Estimate the values of phenobarbital clearance, volume of distribution and half-life in this patient.

\[ \frac{\ln(C_1)}{t_2 - t_1} = \frac{\ln(56)}{24 \times 6} = 0.0087 \text{ h}^{-1} \]

\[ t_{1/2} = \frac{0.693}{k_e} = \frac{0.693}{0.0087} = 79.66 \text{ h} \]

The volume distribution is assumed to be 0.7 L/kg or 49 L for adults

\[ Vd = 0.7 \times 74 = 51.8 L \]

\[ CL = k_e \times Vd = 0.0087 \times 51.8 = 0.45 L/h \approx 0.006 L/kg/h \]

The phenobarbital clearance in this patient is higher than expected value (0.004 L/kg/h).

b. Estimate the expected concentrations at the second time of sampling and compare with the observed concentrations.

\[ CL = 0.004 \times 74 = 0.296 L/h \]

\[ k_e = \frac{CL}{Vd} = \frac{0.296}{51.8} = 0.0057 \text{ h}^{-1} \]

\[ t_{1/2} = \frac{0.693}{k_e} = \frac{0.693}{0.0057} = 121.58 h > \text{observed 79.66 h} \]

\[ C_{ss} = \frac{F \times D}{CL \times \tau} = \frac{1 \times 200}{0.296 \times 24} = 28.15 \text{ mg/L} \]

\[ C = C_{ss} e^{-k_e \times t} = 28.15 \times e^{-0.0057 \times 24 \times 6} = 12.39 \text{ mg/L} < \text{observed 16 mg/L} \]
c. Given that clearance of this drug is much more variable than volume of distribution, state the likely causes of the observations made and provide a recommendation for his future antiepileptic therapy with phenobarbital.

The phenobarbital blood concentration in this patient are higher than expected, however, his clearance and half-life are higher and shorter than expected. One of the most likely reason is the patient took more than prescribed.

The usual steady-state concentration of phenobarbital in adults is 20 mg/L. In order to achieved this concentration in this patient, the maintain dose is calculated below.

\[ D = \frac{C_{ss} \times CL \times \tau}{F} = \frac{20 \times 0.45 \times 24}{1} = 216 \text{ mg/day} \]

So keep the current dose regimen: 200 mg daily.
Question 4

A 49-year old male patient, 83.3 kg in weight, is to receive immediate release carbamazepine regimen.

1) Please compute the daily dose required to achieve a steady state plasma concentration of 7.5 mg/L, assuming monotherapy.

Carbamazepine has a clearance of 0.064 L/kg/h for monotherapy. For immediate release carbamazepine, the oral bioavailability is 0.8

\[
D = \frac{C_{ss} \times CL \times \tau}{F} = \frac{7.5 \times 0.064 \times 83.3 \times 24}{0.8} = 1199.52 \text{ mg/day} \approx 1200 \text{ mg/day}
\]

2) If the patient receives phenobarbital medication of 2.0 mg/kg Q12h for the past 3 months and the doctor decides to include a concomitant therapy of carbamazepine in order to better control his seizure, compute the daily maintenance dose required to attain a target steady state concentration of 7 mg/L carbamazepine, using an immediate release formulation. Later on, over the course of treatment, blood samples were evaluated for carbamazepine and were reported to be 12.5 mg/L. How should his daily dose be adjusted to get to the desired concentration?

Carbamazepine has a clearance of 0.1 L/kg/h for polytherapy. For immediate release carbamazepine, the oral bioavailability is 0.8

\[
MD = \frac{C_{ss} \times CL \times \tau}{F} = \frac{7 \times 0.1 \times 83.3 \times 24}{0.8} = 1749.3 \text{ mg/day}
\]

\[
\frac{MD_1}{MD_2} = \frac{C_{ss,2}}{C_{ss,1}}
\]

\[
\frac{1749.3}{MD_2} = \frac{12.5}{7} \rightarrow MD_2 = 979.6 \text{ mg/day} \approx 1000 \text{ mg/day}
\]
Question 5

V.W., an 8-year old, 25 kg male, is receiving 250 mg of valproic acid q12h for absence seizures. His steady-state trough concentration was 25 mg/L. Because of inadequate seizure control and the lack of apparent side effects, it is decided to increase the trough concentration to 50 mg/L. What dose will be required to achieve the target trough concentration of 50 mg/L if the dosing interval is decreased from q12h to q8h?

The volume distribution is assumed to be 0.14 L/kg.

\[ V_d = 0.14 \times 25 = 3.5 \text{ L} \]

\[ C_{\text{max}} = C_{\text{min}} + \frac{F \times S \times D}{V_d} = 25 + \frac{1 \times 1 \times 250}{3.5} = 96.4 \text{ mg/L} \]

\[ k_e = \frac{\ln\left(\frac{C_1}{C_2}\right)}{t_2 - t_1} = \frac{\ln\left(\frac{96.4}{25}\right)}{12} = 0.112 \text{ h}^{-1} \]

\[ C_{\text{ss, min}} = \frac{C_{\text{ss}} \times e^{-k_e \times \tau}}{1 - e^{-k_e \times \tau}} = \frac{F \times S \times D \times e^{-k_e \times \tau}}{V_d \times \left(1 - e^{-k_e \times \tau}\right)} \]

\[ D = \frac{C_{\text{ss, min}} \times V_d \times (1 - e^{-k_e \times \tau})}{F \times S \times e^{-k_e \times \tau}} = \frac{50 \times 3.5 \times \left(1 - e^{-0.112 \times 8}\right)}{1 \times 1 \times e^{-0.112 \times 8}} = 253 \text{ mg} \approx 250 \text{ mg} \]