1. Baby girl A, 3kg, 15 days, is receiving phenobarbital because of neonatal seizures. An IV loading dose of phenobarbital sodium of 20mg/kg was given followed by maintenance doses of 1.5mg/kg every 12 hours. She has a post-load concentration of 24mg/L at 1 hour after the dose. Calculate the baby’s volume of distribution.

\[
Vd = \frac{D \cdot S \cdot F}{C} = \frac{20mg/\text{kg} \cdot 3\text{kg} \cdot 1 \cdot 0.9}{24\text{mg}/L} = 2.25L \rightarrow 2.25L/3\text{kg} = 0.75L/\text{kg}
\]

Note:
Phenobarbital belongs to anticonvulsant and has a long half-life with 5 days (120h) for adults and 2.5 days (60h) for children.

Bioavailability factor (F) can be assumed to be 1.0 since this is an IV dose and salt factor (S) is equal to 0.9 for phenobarbital sodium.

It is not necessary to use equation \( Vd = \frac{D \cdot S \cdot F}{C/e^{-k \cdot t}} \). Although there is a little difference between the concentration drawn at 1 hour and the \( C_0 \) since very little elimination will occur in such a short time when the drug has a very long half-life.

\( (K=0.693/60h=0.01155h^{-1}, C_0=C/e^{-0.01155*1} \approx 24.28mg/L, Vd=2.224L \) which is very close to 2.25L)

The calculation should be used rather than the estimation from population average volume for neonates which is 0.9L/kg to determine the new dose. (0.9L/kg*3kg=2.7L)

The post-load concentration is ideally taken about 1 hour after the loading dose to avoid any distribution phase.
2. C.B., a 10-year-old, 32 kg female, is receiving valproic acid sprinkles 250 mg (2×125mg) po Q8hr for her seizure disorder. Calculate her valproic acid level at steady state.

Valproic acid is an anticonvulsant drug. CL=0.013L/h/kg for children; 0.008L/h/kg for adults. For bioavailability, except the extended release tablets(F=0.8-0.9), all other forms are 1. Here it is valproic acid sprinkles, F=1.

S=1

\[
Cl = (0.013L/h/kg) \times (32kg) = 0.416L/hr
\]

\[
Cpss = \frac{D \cdot S \cdot F}{Cl \cdot \tau} = \frac{250mg \cdot 1 \cdot 1}{(0.416L/h) \cdot 8h} = 75.12mg/L
\]

In the clinic, valproic acid C<sub>max</sub> < 100mg/L, C<sub>min</sub> > 50mg/L. Here Cpss average is in the range of C<sub>max</sub> and C<sub>min</sub>.
3. D.W. is a 52-year-old, 70kg male with glomerulonephritis. His creatinine clearance is reasonably good, but he has a low serum albumin concentration of 2.0g/dL. D.W. is receiving phenytoin and has a steady-state phenytoin concentration of 7mg/L. What would his plasma phenytoin concentration be observed if his serum albumin concentration is normal? (Phenytoin $f_u = 0.1$, normal serum albumin=4.4g/dL).

Glomerulonephritis is a type of kidney disease that affects the kidneys' filtering function.

$$C_{P_{normal}} = \frac{C_p'}{(1 - f_u) \frac{PatientsAlbu}{NormalAlbu} min} + f_u \left( \frac{7mg/L}{(1 - 0.1) \frac{2.0g}dL + 0.1} \right) = 13.75mg/L$$

This equation is the most useful when a patient has a low serum albumin concentration but does not have a significantly diminished renal function and is not taking other drugs known to displace phenytoin from plasma protein binding sites.

Phenytoin is primarily used as an anticonvulsant and has been used in the treatment of certain types of cardiac arrhythmias.
4. P.G, a 50 years old, 80 kg patient, is to be treated p.o. with sodium phenytoin capsules, calculate the following:
1). The loading dose to produce an initial concentration of 18 mg/L. How would you administer this dose?
2). The daily maintenance dose to produce an average steady state concentration of 15 mg/L.
(Please use the key parameters available in the slides.)

For phenytoin, V_d=0.65 L/kg, K_M=4 mg/L, V_{max}=7 mg/kg/day
F=1, S=0.92

In the clinic, phenytoin C_{max} < 20mg/L, C_{min} > 10mg/L. Here C_{pss} average 15 mg/L is in the range of C_{max} and C_{min}.

1). \[ V_d = 0.65L/kg \cdot 80kg = 52L \]

\[ LD = \frac{C_p \cdot V_d}{S \cdot F} = \frac{18mg/L \cdot 52L}{0.92 \cdot 1} = 1017.39mg \approx 1000mg \]

The 1000mg dose is given orally as a 400mg dose followed by two 300mg doses at 2-hour intervals to decrease the possibility of nausea and vomiting which may be associated with a single large dose.

2).

\[ MD = \frac{V_{max} \cdot C_{p_{ss}} \cdot \tau}{(K_M + C_{p_{ss}}) \cdot S \cdot F} = \frac{7mg/kg/day \cdot 80kg \cdot 15mg/L \cdot 1day}{(4mg/L + 15mg/L) \cdot 0.92 \cdot 1} = 480.55mg \approx 480mg/day \]
5. 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 (dihydrate) infusion of 60 mg/hr. The theophylline concentration was 12mg/L at 10pm and 16mg/L at 3am. Calculate the apparent clearance and half-life of theophylline in M.K. Assume that the desired steady-state plasma theophylline concentration for M.K. is 15 mg/L, determine whether the maintenance dose needs to be adjusted. (Vd = 0.5L/kg)

Status asthmaticus is a sudden intense and continuous aggravation of a state of asthma. It is the most severe form of asthma.

\[ V_d = 0.5L/kg, \quad F = 1, \quad S=0.8 \quad (A) \]

\[ V_d= 0.5L/kg * 60kg = 30L \]

\[
CL = \frac{2 \cdot k_0 \cdot F \cdot S}{V_d} + \frac{2 \cdot V_d \cdot (C_1 - C_2)}{(C_1 + C_2) \cdot (t_2 - t_1)} = \frac{2 \cdot 60mg / h \cdot 1 \cdot 0.8}{(12+16)mg / L} + \frac{2 \cdot 30L \cdot (12-16)mg / L}{(12+16)mg / L \cdot 5h} = 3.43 - 1.71 = 1.72L / h
\]

\[
t_{1/2} = \frac{0.693 \cdot V_d}{CL} = \frac{0.693 \cdot 30L}{1.72L / h} \approx 12h
\]

\[
C_{ss} = \frac{F \cdot S \cdot k_0}{CL} = \frac{1 \cdot 0.8 \cdot 60}{1.72} = 27.91mg / L \rightarrow too \ high
\]

Need to decrease the infusion rate.

If to maintain M.K.'s theophylline level at 15mg/L,

\[
k_0 = \frac{CL \cdot C_{ss}}{F \cdot S} = \frac{1.72L / h \cdot 15mg / L}{1 \cdot 0.8} = 32.25mg / h \approx 32mg / h \quad aminophylline \]

\[
dihydrate.
\]

Note: Chiou equation is used to calculate clearance for constant rate infusion.

Therapeutic plasma concentration is 10-20mg/L for theophylline.