1. Theophylline has a volume of distribution of 0.5 L/kg in children (weight 25 kg) and adults (weight 65 kg). The average total body clearance in children is 0.1 L/h/kg, that in adults is 0.04 L/h/kg.

\[
k = \frac{CL}{V_d}
\]

Child: \( CL = 2.5\text{L/h} \)  
Adult: \( CL = 2.6\text{L/h} \)

\[
k = \frac{0.1}{0.5} = 0.2\text{h}^{-1}
\]

\[
k = \frac{0.04}{0.5} = 0.08\text{h}^{-1}
\]

a. Calculate the average half-life of theophylline in children and adults.

Child: \( t_{1/2} = \frac{0.693}{0.2} = 3.5\text{h} \)

Adult: \( t_{1/2} = \frac{0.693}{0.08} = 8.7\text{h} \)

b. For a therapeutic range of 10-20 µg/ml, what dosing regimens are necessary for an immediate release theophylline product with complete bioavailability to stay within this range at all times (assume instantaneous bolus absorption).

\( \tau = t_{1/2} \)

4h, better 3h  
8h

\[
D = \frac{C_{ss} \cdot CL \cdot \tau}{F}
\]

Child: \( 15 \cdot 2.5 \cdot 3 = 112.5 \text{ mg} \)  
Adult: \( 15 \cdot 2.6 \cdot 8 = 312 \text{ mg} \)

\[
= \frac{15 \cdot CL \cdot \tau}{1}
\]

100 mg q3h  
300 mg q8h
2. How rapidly should the aminophylline loading dose be administered if it is given intravenously?

Theophylline displays two-compartment pharmacokinetics in which the therapeutic or bronchodilating effects correlate more closely with concentrations in the second or tissue compartment. Since the toxic effects of theophylline correlate with high concentrations in the initial volume of distribution, the loading dose is usually infused over 30 minutes to minimize accumulation within the first compartment and to avoid toxicity.
3. The hepatic clearance of a drug in a patient is reduced by 50% due to chronic viral hepatitis. How is the total body clearance of the drug affected? What should be the new dose of the drug in the patient? Assume that renal drug clearance \( fe = 0.4 \) and plasma drug protein binding are not altered.

\[
RL = \text{residual liver function} = \frac{[Cl_h]_{\text{hepatitis}}}{[Cl_h]_{\text{normal}}}
\]

\[
fe = \text{fraction of drug excreted unhanged}
\]

\[
1 - fe = \text{fraction of drug metabolized}
\]

\[
[Cl_h]_{\text{hepatitis}} = RL \cdot [Cl_h]_{\text{normal}}
\]

Substituting for \([Cl_h]_{\text{normal}}\) with \( Cl_{\text{normal}}(1 - fe)\),
\[
[Cl_h]_{\text{hepatitis}} = RL \cdot Cl_{\text{normal}}(1 - fe)
\]

Assuming no renal clearance deterioration due to hepatitis,
\[
Cl_{\text{hepatitis}} = [Cl_h]_{\text{hepatitis}} + [Cl_R]_{\text{normal}} = RL \cdot Cl_{\text{normal}}(1 - fe) + Cl_{\text{normal}} \cdot fe = Cl_{\text{normal}}[RL (1 - fe) + fe]
\]

\[
\text{Dose}_{\text{hepatitis}}/\text{Dose}_{\text{normal}} = [Cl_h]_{\text{hepatitis}}/Cl_{\text{normal}} = RL(1 - fe) + fe
\]

Substituting with \( RL = 0.5 \) and \( fe = 0.4 \):
\[
\text{Dose}_{\text{hepatitis}}/\text{Dose}_{\text{normal}} = [Cl_h]_{\text{hepatitis}}/Cl_{\text{normal}} = 0.3 + 0.4 = 0.7 \text{ (or 70%)}
\]

The adjusted dose of the drug in the hepatic patient would be 70% of the normal subject due to a 50% decrease in hepatic function in the above case \( fe = 0.4 \).
4. When should plasma samples for theophylline concentrations be obtained for a patient who is on an oral regimen with a constant dosing interval?

Plasma samples should be obtained immediately before a scheduled dose because trough concentrations are more predictable than peak concentrations. Peak plasma concentrations can be delayed by slow absorption, resulting in substantial error.

Since the theophylline half-life is short in many patients, the difference between the trough and peak concentrations can be substantial. Theophylline toxicity frequently occurs when the dose is increased to bring trough concentrations into the usually accepted therapeutic range of 10 to 20 mg/L. Such toxicity may be prevented by estimating the peak plasma concentration. Adding the increment in plasma concentration that will be produced by each dose to the observed trough concentration usually will give a reasonable approximation of the peak plasma concentration.