Drug Y is administered via IV infusion at 300 mg to RH, a 55-year old patient with 72 kg body weight. The average steady-state concentration of Drug Y is approximately 160 ng/mL. What would be an appropriate oral dose of Drug Y so that RH’s average blood concentration at steady-state is approximately 215 ng/mL. Assume that oral bioavailability of Drug Y is 0.4 and the dosing interval for IV infusion and oral dosing are the same. (1 pts)

We are given the information that the dosing intervals are the same for both routes of administration. In that case, the average drug concentration is proportional to the area under the curve.

So we use the bioavailability ratio such that

\[
\frac{Dose_{iv}}{Concentration_{iv}} = \frac{Dose_{oral} \times F}{Concentration_{oral}}
\]

\[
Dose_{oral} = \frac{300 \times 215}{160 \times 0.4} = 1007.8 \text{ mg} \sim 1000 \text{ mg}
\]
A patient was administered 800 mg of Drug X over 20 min (iv infusion) from 9:40 to 10:00 am. The serum levels of Drug X were measured at specific time: 24.3 μg/mL at 11:00 am and 5.3 μg/mL at 10:00 am the following day. Assuming **STEADY-STATE** with interdosing interval of 36 h and a one-compartment body model for Drug X, compute the following:

(1) Elimination rate constant (1 pt)

The stop of infusion is 10:00 am and is designated as time 0.

At 1 h (11:00 am), \( C(t=1) = 24.3 \) μg/mL

At 24 h (10:00 am the following day), \( C(t=24) = 5.3 \) μg/mL

\[
k_e = \frac{-\ln(24.3) - \ln(5.3)}{1 - 24} = 0.0662 \text{ } 1/h
\]

(2) Half-life (0.5 pt)

\[
t_{1/2} = \frac{0.693}{k_e} = \frac{0.693}{0.0662} = 10.5 \text{ } h
\]

(3) Peak drug concentration at 10:00 am of the same day of dosing (0.5 pt)

\[
C(t) = C(t = 0)\exp(-k_e t)
\]

\[
C(t = 0) = \frac{24.3}{\exp(-0.0662 \times 1)} = 26.0 \text{ } \mu g/mL
\]

(4) Drug concentration at 9:30 pm of the following day (0.5 pt)

9:30 pm the following day corresponds to \( t = 35.5 \) h

\[
C(t = 35.5) = 26 \exp(-0.0662 \times 35.5) = 2.5 \text{ } \mu g/mL
\]

(5) The volume of distribution (1 pt)

\[
Cp_{min} = 26 \exp(-0.0662 \times 36) = 2.77 \text{ } \mu g/mL
\]

We shall use the following equation to compute \( V_d \):
\[ V_d = \frac{Dose}{k_e T} \cdot \frac{(1 - e^{-k_e T})}{C_{p_{max}} - (C_{p_{min}})e^{-k_e T}} \]
\[ = \frac{800}{0.0662 \cdot 0.333} \cdot \frac{1 - \exp(-0.0662 \cdot 0.333)}{26 - 2.77 \exp(-0.0662 \cdot 0.333)} = 34 \text{ L} \]

(6) The drug clearance (1 pt)

\[ C_{p_{max}} = \frac{D}{CL \cdot T} \cdot \frac{(1 - \exp(-k_e T))}{(1 - \exp(-k_e \tau))} \]
\[ CL = \frac{D}{C_{p_{max}} \cdot T} \cdot \frac{(1 - \exp(-k_e T))}{(1 - \exp(-k_e \tau))} = \frac{800}{26 \cdot 0.333} \cdot \frac{1 - \exp(-0.0662 \cdot 0.333)}{1 - \exp(-0.0662 \cdot 36)} = 2.22 \text{ L/h} \]

Notice that the clearance computed from the equation above is close to the one below:

\[ CL = k_e \cdot V_d = 0.0662 \cdot 34 = 2.25 \text{ L/h} \]
Phenobarbital is an inducer of drug metabolic enzymes. When propranolol, a high-extraction drug, is combined with phenobarbital, what is expected of the half-life of propranolol. Show equation(s) as evidence to support your claim. (2 pt)

Given that propranolol is a high-extraction drug,

\[ CL = Q \]

Consequently, the half-life is independent of intrinsic clearance:

\[ t_{1/2} = \frac{0.693 \cdot V_d}{Q} \]

One would expect no change in the half-life of propranolol when phenobarbital is co-administered.
Drug Z is eliminated entirely by the liver (hepatic metabolism), with a clearance of 75 L/h in subjects with an average liver blood flow of 80 L/h. Estimate the clearance in congestive heart failure patients with a liver blood flow of 50 L/h, assuming no change in hepatic extraction ratio. (2.5 pt)

\[
E = \frac{CL_{intf_u}}{Q_h + CL_{intf_u}}
\]

\[
CL = E \cdot Q_h = \frac{Q_h \cdot CL_{intf_u}}{Q_h + CL_{intf_u}}
\]

\[
75 = \frac{80 \times CL_{intf_u}}{80 + CL_{intf_u}}
\]

\[
CL_{intf_u} = 1200 \text{ L/h}
\]

With the new liver flow rate of 50 L/h,

\[
E(\text{new}) = \frac{CL_{intf_u}}{Q_h + CL_{intf_u}}
\]

\[
E(\text{new}) = \frac{1200}{1200 + 50}
\]

\[
E(\text{new}) = 0.96
\]

\[
CL_h = 0.96 \times 50 = 48 \text{ L/h}
\]

Given the high extraction ratio, one can also assume a negligible change with a decrease in liver blood flow and use the following equation:

\[
CL_h = Q_h \times E
\]

\[
E = \frac{CL_h}{Q_h} = \frac{75}{80} = 0.9375
\]

\[
CL_h = Q_h \times E = 50 \times 0.9375 = 46.9 \text{ L/h}
\]