1. L.J., a 30 year old male, was diagnosed congestive heart failure (CHF). He is 5’9” tall and weighs 80 kg. He was given Furosemide to control CHF symptoms. After a couple of days, his physician found that the diuretic therapy cannot control L.J.’s CHF, and L.J. also suffers cardiac arrhythmia. The physician decided to give L.J. Lanoxin® (Digoxin) tablets and Isoptin® (Verapamil) tablets. In order to achieve the therapeutic concentration of Lanoxin® (1.5 ng/mL), what would be a suggested loading and maintenance dose regimen for Digoxin? (L.J.’s serum creatinine concentration is: 1.4 mg/dL) (Tablets for Digoxin 0.5 mg/0.25mg/0.125mg, and assuming Digoxin is rapidly absorbed.)

Answer:

Given information:
Male with CHF, 30 yrs, 5’9”, 80 kg, \(C_{\text{pCreat}}=1.4\text{mg/dL}\)
Bioavailability for Digoxin Tablets: 0.7
Clearance-factor: 0.75 from verapamil’s effect
\(IBW=50\text{kg} + 2.3\text{kg} \cdot (\text{Height} - 5')\)
IBW=50kg + 2.3 \cdot (9) = 70.7 kg \(\rightarrow\) TBW<1.2 IBW

\[Cl_{\text{creat}}(\text{male}) = \frac{(140 - \text{age}) \cdot \text{weight}}{(72) \cdot C_{\text{pCreat}}}\]

\[Cl_{\text{creat}}(\text{male}) = \frac{(140 - 30) \cdot 80}{(72) \cdot 1.4} = 87.3 \text{ (mL/min)} \text{ (Use TBW for CL}_{\text{Creat}}\text{)}\]

\[CL_{\text{Digoxin}} = 0.33mL / kg / \text{min} \cdot IBW + 0.9 \cdot Cl_{\text{creat}}(\text{with - CHF})\]

CL=0.33\cdot70.7+0.9\cdot87.3=101.9 (mL/min) \(\leftarrow\) without Verapamil

CL=CL-0.75=76.43 (mL/min) \(\leftarrow\) with Verapamil

\(V_{\text{Digoxin}} = 3.8L / kg \cdot IBW + 3.1 \cdot Cl_{\text{creat}}\)

Vd=3.8\cdot70.7+3.1\cdot87.3=539.3 (L)

1.5 ng/mL=1.5 ug/L

To obtain an initial concentration of 1.5 ug/L, \(C_{p0} = \frac{D \cdot F}{V_{d}}\)

LD = \(C_{p0} \cdot Vd/F = (1.5 \text{ ug/L})(539.3 \text{ L})/0.7 = 1155.6 \text{ ug} \sim 1125 \text{ ug} (2*500ug + 1*125ug)\)

A maintenance dose to provide the same concentration is:

\[MD = Cl \cdot \overline{C_{\text{pss}}} \cdot \tau / F = (110.1 \text{ L/day})(1.5 \text{ ug/L})(1 \text{ day})/0.7 = 235.9 \text{ ug/day} \sim 250 \text{ ug/day}\]
2. A recent study was performed to evaluate Ritonavir’s effect on Digoxin pharmacokinetics. Six healthy subjects in the treatment group were given Ritonavir for 2-days until steady state of Ritonavir was reached, and the other 6 subjects in the control group were given placebo for 2 days. On day 3, all subjects were given a dose of Digoxin of 0.5 mg. Then blood samples were taken based on designed time points. The quantified digoxin concentrations were plotted with time in the following graph. Table I shows the noncompartmental analysis results. (Ritonavir is a HIV protease inhibitor, and also inhibits metabolism enzymes (CYP450), and P-gp in the renal tubule.) State whether the following statement is TRUE or FALSE? And Why?

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Ritonavir</th>
<th>Wilcoxon test</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-∞} (h·ng/mL)</td>
<td>22 ± 9</td>
<td>41 ± 17</td>
<td>P &lt; .01</td>
</tr>
<tr>
<td>Cl_{total} (mL/min)</td>
<td>409 ± 30</td>
<td>238 ± 29</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Cl_{renal} (mL/min)</td>
<td>194 ± 23</td>
<td>126 ± 21</td>
<td>P &lt; .01</td>
</tr>
<tr>
<td>Cl_{total} (mL/min)</td>
<td>215 ± 15</td>
<td>112 ± 7</td>
<td>P &lt; .01</td>
</tr>
<tr>
<td>V_{dss} (L)</td>
<td>255 ± 47</td>
<td>451 ± 60</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>A_t20 (μg)</td>
<td>273 ± 25</td>
<td>295 ± 33</td>
<td>P = .15</td>
</tr>
<tr>
<td>t_{1/2α} (h)</td>
<td>16 ± 3</td>
<td>41 ± 9</td>
<td>P &lt; .01</td>
</tr>
<tr>
<td>t_{1/2α} (h)</td>
<td>45 ± 3</td>
<td>57 ± 6</td>
<td>P = .05</td>
</tr>
</tbody>
</table>

AUC_{0-∞}, Area under plasma concentration-time curve from time 0 to infinity; Cl_{total}, total clearance; Cl_{renal}, renal clearance; Cl_{nonrenal}, nonrenal clearance; V_{dss}, volume of distribution at steady state; A_t20, amount excreted into urine from time 0 to infinity; t_{1/2α}, terminal elimination half-life in plasma; t_{1/2ur}, terminal urinary excretion half-life determined by excretion rate versus time plot; t_{1/2e}, terminal urinary excretion half-life determined by amount remaining to be excreted versus time plot.

A: Digoxin could be partially eliminated by P-gp mediated renal tubular secretion.
B: Ritonavir had a profound impact on Digoxin distribution.
C: Digoxin clearance and volume of distribution need to be corrected by some factor when Digoxin and Ritonavir are co-administered and standard equations for Digoxin clearance and volume of distribution.
D: Ritonavir and Quinidines have the same effect on the volume of distribution of Digoxin.
E: Toxicity is not an issue when Digoxin and Ritonavir are co-administered.

Answer:
A: True, Ritonavir inhibits P-gp in renal tubule, and Digoxin could be also eliminated by P-gp mediated renal tubular secretion as the renal clearance for digoxin decreases when Ritonavir is co-administered and Digoxin is a P-gp substrate.
B: True, Ritonavir increases digoxin volume of distribution dramatically.

C: True, Base on the graph and table, it is clearly shown that Ritonavir could decrease Digoxin Total clearance, renal clearance, and increase volume of distribution. Ritonavir has great impacts on both elimination and distribution of Digoxin. Thus, standard equation for Digoxin clearance and volume of distribution is not suitable, similar to Quinidine, but Quinidine decreases the volume of distribution of Digoxin.

D: False, See C.

E: False, Digoxin concentration could exceed its therapeutic window, resulting in toxicity when total clearance of Digoxin decreases.
3. In a clinical study to assess effects of St. John's Wort (*Hypericum perforatum*) on Tacrolimus Pharmacokinetics, subjects received St. John's wort (300 mg orally three times daily) for 18 days. On day 19, subjects started to receive multiple oral doses of tacrolimus (3 mg Q12h PO). Subject#1, a male, 45 year old, weights 60 kg. On day 30, this subject’s peak and trough concentration (before next dose) were measured, which is 10 ng/mL and 3 ng/mL. Is there any impact from the St. John’s Wort on Tacrolimus Pharmacokinetics? Why? (assume CL: 0.06 L/h/kg, and Tacrolimus is rapidly released and absorbed into system.)

**Answer:**

Given information:

- Male: 45 yr, 60kg
- Dose: 3 mg Q12h PO (Bioavailability: 0.25)
- CL: 0.06L/h/kg
- Vd: 1 L/kg

\[
CL = 0.06L/h/kg \cdot 60kg = 3.6L/h
\]

\[
Vd = 1L/kg \cdot 60kg = 60L
\]

\[
Ke = CL/Vd = 3.6/60 = 0.06(1/hr)
\]

\[
C_{min} = \frac{F \cdot S \cdot D \cdot e^{-\text{Ke} \cdot \tau}}{Vd \cdot (1 - e^{-\text{Ke} \cdot \tau})} = 0.012mg/L = 12ng/mL >> 3ng/mL
\]

\[
C_{max} = \frac{0.25 \cdot 3 \cdot e^{-0.06 \cdot 12}}{60 \cdot (1 - e^{-0.06 \cdot 12})} = 0.024mg/L = 24ng/mL >> 10ng/mL
\]

This indicates that St. John’s Wort could decrease drug concentrations due to its induction effect.
4. R.J, a 70 kg male patient (5'6", 45 year old, $C_{pCreat} \ 1.3 \text{ mg/dL}$) received a 30 mg methotrexate loading dose iv followed by a 45 mg/h infusion over 36 hours. At 36 h, leucovorin rescue (10 mg/m² q6h) was started. Make a recommendation how to continue therapy. When do you expect the methotrexate level to fall below 0.1 μM?

Answer:

Given Information:
Male, 70kg, 45 yr, 5’6”, $C_{pCreat}$ 1.3 mg/dL
Dose: 30 mg LD + 45 mg/h IV

$IBW = 50kg + 2.3kg \cdot (Height - 5')$

IBW=50kg + 2.3· (6) = 63.8 kg $\Rightarrow$ TBW<1.2IBW

$CL_{creat} (male) = \frac{(140 - age) \cdot weight}{(72) \cdot C_{pCreat}}$

$CL_{creat} (male) = \frac{(140 - 45) \cdot 70}{(72) \cdot 1.3} = 71.05$ (mL/min) (Use TBW for CL$_{Creat}$)

CL=1.6·71 =113.6(mL/min)=6.82(L/hr)

$C_{Pss} = \frac{R_0}{Cl}$

$C_{Pss}=45/6.82=6.6$(mg/L)$=6.6/0.454=14.5uM$

$k_1 = \frac{0.693}{t_{1/2(α)}} = \frac{0.693}{3} = 0.231h^{-1}$

$t$ for 0.5 μM: $t = \frac{\ln(0.5)}{0.231} = 14.6h \rightarrow at (14.6 + 36) = 50.6h$

$k_2 = \frac{\ln(2)}{t_{1/2(β)}} = \frac{\ln(2)}{10} = 0.0693h^{-1}$

$t$ for 0.1 μM: $t = \frac{\ln(0.1)}{0.0693} = 23.2h \rightarrow at (50.6 + 23.2) = 73.8 h$