Designing Schedule and Dosages of Diuretics and the other drug

Fan Yang, Jiayun Zhong and Rongke Lyu
Introduction

The mechanism of action of diuretics is to promote kidney function as a way of removing water and sodium from the circulatory system. Due to this principle, diuretic will promote a more rapid removal of both drugs. The other drug will then be eliminated more rapidly and have a shorter effective time. By using our model and researching the literature we find that we need to adjust both the schedule and dosages of the other drug to keep both drugs effective and safe.
We assume:

1) a patient will inject diuretic for heart disease and take 1 pill of the other drug orally for another disease (which contains 400 mg or $4 \times 10^5$ ug effective ingredient of drug B) per day on a normal base;

2) the patient drinks water in the same rate as he/she gets rid of water;

3) the patient’s blood volume is constant without taking any drugs.

Also, for the removal of drug, we ignore the distribution in blood and only consider the clearance from the blood.
Process of modeling

A normal person......

Reference coefficient:
Liquid in = a mL/min
Liquid out, normal = a mL/min
Liquid out, after diuretic = b mL/min
Blood volume = V mL
Safe concentration = m µg/mL
Effective concentration = n µg/mL

Reference variable:
Amount of drug B in blood: x
Total time: T
Time after taking diuretic: t
A patient takes drug B 1 pill / day......

Reference coefficient:
Liquid in = a mL/min
Liquid out, normal = a mL/min
Liquid out, after diuretic = b mL/min
Blood volume = V mL
Safe concentration = m µg/mL
Effective concentration = n µg/mL

Reference variable:
Amount of drug B in blood: x
Total time: T
Time after taking diuretic: t
Reference coefficient:
- Liquid in = a mL/min
- Liquid out, normal = a mL/min
- Liquid out, after diuretic = b mL/min
- Blood volume = V mL
- Safe concentration = m µg/mL
- Effective concentration = n µg/mL

Reference variable:
- Amount of drug B in blood: x
- Total time: T
- Time after taking diuretic: t

Concentration C(T) v.s. Time T in the patient’s body
A patient takes drug B 1 pill / day + Inject diuretic at time $T_0$ ($t = 0$)

Reference coefficient:
- Liquid in = $a$ mL/min
- Liquid out, normal = $a$ mL/min
- Liquid out, after diuretic = $b$ mL/min
- Blood volume = $V$ mL
- Safe concentration = $m$ µg/mL
- Effective concentration = $n$ µg/mL

Reference variable:
- Amount of drug B in blood: $x$
- Total time: $T$
- Time after taking diuretic: $t$
A patient takes drug B 1 pill / day + Inject diuretic at time $T_0$ ($t = 0$)

When $T = T_0$, $t = 0$:

$$x(t) = \text{amount of drug B in the body}$$

$$x'(t) = \text{rate in} - \text{rate out}$$

Rate in = \frac{a \text{ mL/min}}{} \cdot \frac{0 \text{ ug}}{\text{mL}} = 0 \text{ ug/min}$$

$$\text{Rate out} = \frac{x(t) \text{ ug}}{[V - (b - a)t] \text{ mL/min}} \cdot \frac{b \text{ mL/min}}{} = \frac{x(t) \cdot b}{V - (b - a) \cdot t}$$

$$\frac{dx}{dt} = 0 - \frac{x(t) \cdot b}{V - (b - a) \cdot t}$$
Amount:

\[ x(t) = \frac{1}{b} \sqrt{\frac{[V - (b - a) * t]^\frac{1}{b-a} * x_0^\frac{1}{b}}{V^\frac{1}{b-a}}} \]

Concentration:

\[ C(t) = \frac{1}{b} \sqrt{\frac{[V - (b - a) * t]^\frac{1}{b-a} * x_0^\frac{1}{b}}{V^\frac{1}{b-a}}} \]

Combine the concentration of drug-B-only curve with the concentration-influenced-by-diuretic equation, we can get the overall concentration curve vs. T.

**Reference coefficient:**
- Liquid in = a mL/min
- Liquid out, normal = a mL/min
- Liquid out, after diuretic = b mL/min
- Blood volume = V mL
- Safe concentration = m µg/mL
- Effective concentration = n µg/mL

**Reference variable:**
- Amount of drug B in blood: x
- Total time: T
- Time after taking diuretic: t
Additional condition 1: intravenous fluid therapy

- Fluid introduced at a constant rate $c$ mL/min
- Fluid out will change to $d$ mL/min consequently

\[\begin{align*}
0 \text{ µg/mL} & \quad \rightarrow \quad x_0 \text{ µg} \\
V \text{ mL} & \quad \rightarrow \quad d \text{ mL/min}
\end{align*}\]
Amount:

\[ x(t) = \frac{1}{b} \sqrt{\frac{[V - (d - c)t]^{\frac{1}{d-c}} x_0^{\frac{1}{d}}}{\frac{1}{V^{d-c}}}} \]

Concentration:

\[ C(t) = \frac{1}{b} \sqrt{\frac{[V - (d - c)t]^{\frac{1}{d-c}} x_0^{\frac{1}{d}}}{\frac{1}{V^{d-c}}}} \cdot \frac{1}{6000 - (d - c)t} \]
Additional condition 1: intravenous fluid therapy
Additional condition 2: drink large amount of water at regular time interval

- The concentration of drug B will drop to a low level immediately after drinking water.
- Then with the decrease of fluid in the body, the concentration will approach the concentration level of drug B influenced by the diuretic.
Drink large amount of water at regular time interval

- Drug-B-only mass
- Drug-B-influenced-by-diuretic mass

mass (ug) vs. time (min)
Now we put in specific data to the model

An 80 kg male adult

According to the reference papers:

Liquid in = \(a\) mL/min = 1.5 mL/min

Liquid out, normal = \(a\) mL/min = 1.5 mL/min

Liquid out, after diuretic = 2.2 mL/min

Blood volume = 6000 mL

Safe concentration = \(m\) µg/mL = 65 µg/mL

Effective concentration = \(n\) µg/mL = 18 µg/mL
Amount: 

\[ x(t) = \frac{1}{2.2} \sqrt{\frac{(6000 - 0.7t)^{0.7} \cdot x_0^{1.2}}{6000^{0.7}}} \]

Concentration: 

\[ C(t) = \frac{1}{2.2} \sqrt{\frac{[6000 - 0.7t]^{0.7} \cdot x_0^{1.2}}{V^{0.7}}} \]
For convenience, we transfer all the concentration to the amount:

1. After the injection of the diuretic, the **effective value** $= 18 \times (6000 - 0.7t)$

2. After the injection of the diuretic, the **safe value** $= 65 \times (6000 - 0.7t)$

3. The amount of drug B in the body (if only taken drug B) $= C \times 6000$
Because diuretic will influence human body at least 8 hours, so the latest time to take diuretic is

\[ T = 16 \text{hr} \times 60 \text{min/hr} = 960 \text{ min} \]

Take 30 minutes as a period, we generate one graph for each \( T_0 \) (time inject diuretic) between

\( T_0 = 30 \) and \( T_0 = 960 \). (\( T_0 = 30 \), \( T_0 = 60 \), \( T_0 = 90 \) …… \( T_0 = 960 \))
Example:

- **Effective amount**
- **Safe amount**
- **“Drug-B-only” amount**
- **After affected by diuretic**
- **Influence of the diuretic**
Analysis and discussion

Intersection: concentration of drug B is effective level before the intersection and it is ineffective after the intersection

(a) Injection after 30 mins: the earliest point that we can inject diuretic
Analysis and discussion

Intersection: concentration of drug B is effective level before the intersection and it is ineffective after the intersection.

(b) Injection after 60 mins: typical situation when we inject diuretic in the time period [0,240]
Analysis and discussion

Intersection: concentration of drug B is effective level before the intersection and it is ineffective after the intersection

(c) Injection after 240 mins: injecting diuretic at the highest concentration point
Analysis and discussion

(d) Injection after 600 mins: typical situation when we inject diuretic in the time period [240, 960], that is the period when the concentration of drug B decreases.

Intersection: concentration of drug B is effective level before the intersection and it is ineffective after the intersection.
Analysis and discussion

Intersection: concentration of drug B is effective level before the intersection and it is ineffective after the intersection.

(e) Injection after 960 mins: the latest point we can inject the diuretic.
The first solution:

First solution:
- Take constant amount of drug B
- Change the time when the person takes the next dose drug B

Maximum amount under the safe line
- If we assume the accumulation of drug B is very small
- The accumulation will make the peak increases at the first few days
- Then the peak become stable

Take the second pill of drug B 1185 minutes (19.75 hours) after his first pill
The second solution:

- Take drug B with constant time interval, 24 hours
- Change the amount of drug B taken each time

Maximum amount under the safe line

- The accumulation will make the peak increases at the first few days
- We change the amount according to pharmacokinetics equation of drug B
- Then the peak become stable

Take the second pill of drug B 1440 minutes (24 hours) after his first pill
Improvement

1. Diuretics can increase the blood speed and the removal rate of diuretics. If we can get the experimental data of the increased removal rate, we can incorporate this factor and generate a more accurate function of blood concentration of drug B after diuretics injection.

2. We choose drug B because it does not interact with diuretics. Other drugs may interact with diuretics. Eg. Estrogen can decrease the diuretic effect. Dopamine can increase the diuretic effect.

3. If we incorporate the effects of antidiuretic hormone on the urine output rate, the graph of drug B concentration will change after the release of antidiuretic hormone.

4. The diuretic will decrease the sodium and potassium amount. The sodium enhances water retention while potassium enhances water removal from the body. If we have exact amounts change of sodium and potassium, we can generate a more accurate modeling.
We would be glad to answer questions or engage in conversation.

Thank you for your attention.