Executive Summary

Statement of Problem: Design a schedule and dosage of two drugs.

Introduction

We assume a patient will inject diuretic for heart disease and take 1 pill of drug B orally for another disease (which contains 400 mg = 4 * 10^5 μg effective ingredient of drug B) per day on a normal base. The concentration of the diuretic peaks at the same time of injection. Since drug B is taken orally, its concentration increases at first and decrease after the peak.

We first find separate equations for:
1) taking the drug B only and
2) effect of diuretic on a certain amount of drug B.

Then we combine 2 curves together. As for the removal of drug, we ignore the distribution in blood and only consider the clearance from the blood.

To counteract the fluid loss due to diuretic, we either give additional fluids through intravenous fluid therapy, or make the patient regularly drink large amount of water.

Process of Modeling

1. We assume a person drinks a mL water per minute and gets rid of a mL water (through urine, sweating, breath) per minute, so the person has a constant blood volume V mL.
2. The patient takes drug B to cure a certain disease. We plot points to generate the blood concentration of drug B: C(T) within 24 hours. Range of T: [0,1440 minutes]. Effective and safe range of C(T): [n,m].

3. The patient takes diuretic through injection. At time T_0, the concentration of drug B in his body is C_0 μg/mL. the amount of the drug x_0 = C_0 * V.
4. The patient intakes water at a constant rate (a mL/min). Since diuretic will increase the urine output of the body to b mL/min in the same period of time, 24h Assume t minute passes after the injection of diuretic.
5. The concentration will be:
\[
C(t) = \frac{\frac{1}{\sqrt{V}} \left[ V - (b - a) \cdot t \right] \left[ \frac{1}{b-a} * x_0 \right]^\frac{1}{2}}{V - (b - a) \cdot t}
\]

V is blood volume, a mL/min is normal fluid in and out, b mL/min is fluid out after taking diuretic (b > a), t is the time after injecting diuretic, T is the total time passed.

6. We combine the pharmacokinetics equation of drug B with the C(t). Now we use specific data to illustrate the pharmacokinetics equation of drug B with the C(t).

A man with 6000 mL blood, \(V = 6000 \) mL whose water intake and output is 2160 mL, so \(a = 1.5 \) mL/min. After taking 60 mg furosemide, there will be increase of 1008 mL urine, so \(b = 2.2 \) mL/min. We assume the effective concentration of drug B is 18 \(\mu\)g/mL \((n = 18 \mu\)g/mL\) and the safe value is 65 \(\mu\)g/mL \((m = 65\mu\)g/mL\).

\[
C(t) = \sqrt[\frac{\frac{1}{\sqrt{V}} \left[ 6000 - 0.7t \right] \left[ \frac{1}{0.7} * x_0 \right]^\frac{1}{2}}{6000 - 0.7t}}
\]

7. For convenience of calculation, we transform all the concentration of drug B to mass of drug B in the body. In the period of 1440 minutes (one day), we need to keep the mass of drug B (under the influence of the diuretic) between the effective and safe value. Also, the diuretic affects the body at least 8 hours (480 minutes), so the latest time of taking diuretic is \(T = 16\) h, or \(T = 960\) minutes. Take 30 minutes as a period, we modeled the time that the mass of drug drops to the effective value under the influence of diuretic when the patient gets diuretic injection at \(T = 30, 60, 240, 600, 960\) minutes. At each condition, the time that mass of drug B drops to the effective value is also the time that a patient needs to take drug B again.

8. We first use intravenous injection to counteract the diuretic. The water intake rate is constant, c ml/min. We assume the urine output is constant, d ml/min. Therefore, our model is the same as the model in procedure 5.

The concentration of drug B is:

\[
\chi(t) = \frac{\frac{1}{\sqrt{V}} \left[ V - (d - c) \cdot t \right] \left[ \frac{1}{d-c} * x_0 \right]^\frac{1}{2}}{V \left[ \frac{1}{d-c} \right]}
\]

9. We then ask the patient to drink a large amount of water at regular time interval. After each intake of water, the blood volume increase rapidly at first and then equals to the amount of water intake. We assume the increase happens in extremely short amount of time as soon as the patient drink water. The blood volume becomes \(V + f\) when the patient drink water and stay constant until the next time he drinks water. Therefore, we generate the concentration of drug B.

**Analysis and discussion**

1. Graph (a) stands for the earliest point that we can inject diuretic; Graph (b) stands for the typical situation when we inject diuretic in the time period \([0,240]\), that is the period when the concentration of drug B rises; Graph (c) stands for injecting drug at the highest concentration
point; Graph (d) stands for the typical situation when we inject diuretic in the time period [240, 960], that is the period when the concentration of drug B decreases; Graph (e) stands for the latest point we can inject the diuretic.

2. Diuretics will increase the clearance rate of drug B from the body and change the peak concentration of drug B. To keep the concentration between the effective and the safe level in one day, 24 hours, we have two solutions:
   a) Take constant amount of drug B as usual and change the time T0 when the person takes drug B. On each graph, we mark the intersection point between the concentration of drug B and the effective line. Under this situation, since the patient takes same amount of drug B every day, and the maximum amount will not exceed the safe line, at the marked point, person A should take the second pill of drug B to prevent its amount from dropping below the effective line.
      For example, if the person inject diuretic after one hour he took drug B, (graph (b) ), he needs to take the second pill of drug B 1185 minutes (19.75 hours) after his first pill instead of taking it 24 hours after the first pill.
   b) Take drug B with constant time interval, 24 hours, and change the amount of drug B taken each time. In this case, we need to concern whether the max value of the concentration will exceed the safe line. If we have the specific drug pharmacokinetics equation of the drug B, we can calculate how much more drug B the patient will take based on when he injects the diuretic.

**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.
Appendix

\( x(t) \) = amount of drug B in the body

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

rate in = \( \frac{a \, ml}{min} \times \frac{0 \, ug}{ml} = 0 \, ug/min \)

rate out = \( \frac{x(t) \, ug}{[V-(b-a)t] \, ml} \times \frac{b \, ml}{min} = \frac{x(t)+b}{V-(b-a) \times t} \)

Thus, \( \frac{dx}{dt} = 0 - \frac{x(t)+b}{V-(b-a)+t} \)

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

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

a) After the injection of the diuretic, the effective value = 18*(6000-0.7t)
b) After the injection of the diuretic, the safe value = 65*(6000-0.7t)
c) The mass of drug B in the body (if only taken drug B) = C*6000

a. Inject diuretic at T=30 minutes(half an hour) :
b. Inject diuretic at $T=60$ minutes (1 hour):

![Graph showing mass over time for diuretic injection at 60 minutes.](image1)

$$X: 11.80$$
$$Y: 0.359 \times 10^4$$

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c. Inject diuretic at $T=240$ minutes (4 hours) when the drug $B$ is at the highest concentration in the original curve:

![Graph showing mass over time for diuretic injection at 240 minutes.](image2)

$$X: 1036$$
$$Y: 9.709 \times 10^4$$
d. Inject diuretic at T=600 minutes (10 hours):
Inject diuretic at T=960 minutes (16 hours), which is the latest time to inject the diuretic:
References


