Day 4: Dosing Schedules

Pharmacokinetic information for some drugs

	terfenadine (no juice)	terfenadine (with juice)	cisplatin
Half-life, $t_{1/2}$ (hrs)	8.2	16	58
Time constant, τ (hrs)			
Absorption time, t_0 (hrs)	1 (oral)	1 (oral)	0.45 (i.v.)
Effective Level, EL (mg/L)	52	52	0.008
Toxic Level, TL (mg/L)	188	188	0.012

Data Analysis

In the 1990's, the antihistamine terfenadine was linked to several cases of cardiac arrhythmia and even cardiac arrest. In a few instances, the victims had habitually drunk grapefruit juice, which contains several compounds that bind to the enzyme CYP3A4. When CYP3A4 is inhibited, elimination of terfenadine slows down dramatically (see table below).[1] Terfenadine was eventually replaced with fexofenadine, which has all the properties of terfenadine but does not require CYP3A4 to break down.

1. A convenient dosing schedule is to take the drug twice a day, every 12 hours. What is a good prescription for a 53-kg patient who doesn't drink grapefruit juice? Describe the dosing schedule using the parameters dose (D) and period (T). Prepare a plot to illustrate that your dosing schedule is safe and effective.

2. Design a dosing schedule that is both safe and effective for both grapefruit and non-grapefruit drinkers. Play it safe: keep the concentration below 75% of the toxic level. What are D and T?

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[1] C.P. Clifford *et al*, 1997, *European Journal of Clinical Pharmacology 52*, 311–315.

Exercise

Cisplatin is a platinum-containing compound used in chemotherapy. Like most chemotherapy drugs, cisplatin is not very selective: it attacks both healthy cells and cancerous cells. For this reason, its toxic level is close to its effective level. During the dosing schedule, the cisplatin concentration is often close to the toxic level, which leads to the nausea, vomiting, and weight loss that cancer patients suffer.
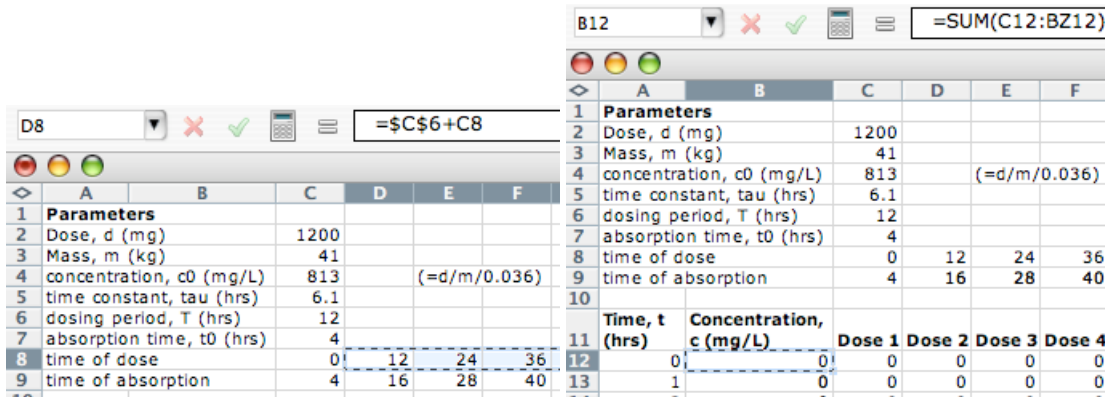
3. Design a dosing schedule that is safe and effective for a 75-kg patient. The chemotherapy will last for two weeks or more, and it is okay if the concentration is below the effective level for the first few days, as long as it is never above the toxic level. Specify D and T.

Acetaminophen has a half-life of 2.5 hours, is absorbed within a half-hour after ingestion, and comes in 500-mg tablets. It's effective level varies with each person, but a range of 50–80 mg/L covers most people. Similarly, the toxic level for any person could fall in a range of 250–400 mg/L. Because of this variability, the dosing period must be frequent enough (six hours or less) that the patient can decide if the first dose is enough (*i.e.*, is above the effective level) or if a second dose is required.

4. If a 60-kg person is very sensitive to acetaminophen, how often should this person take each tablet?

5. If a 60-kg person is relatively insensitive to acetaminophen, how often should this person take each tablet? Would it make sense to take two tablets instead, half as often?

Tutorial: Multiple-Step Dosing Schedule

1. Open your Excel file from Day 3, and copy the sheet to a new one. We will modify your model from Day 3 for a multiple-step dosing schedule.

2. Select row 6 and insert a new row. Define a new parameter: dosing period T.

3. Change the definition of the parameter "time of dose" in cell D8. Use an equation that refers to the dosing period.

| B12 | ▼ | ✕ | ✓ | ▦ | ≣ | =SUM(C12:BZ12) |

	A	B	C	D	E	F
1	Parameters					
2	Dose, d (mg)		1200			
3	Mass, m (kg)		41			
4	concentration, c0 (mg/L)		813		(=d/m/0.036)	
5	time constant, tau (hrs)		6.1			
6	dosing period, T (hrs)		12			
7	absorption time, t0 (hrs)		4			
8	time of dose		0	12	24	36
9	time of absorption		4	16	28	40
10						
11	Time, t (hrs)	Concentration, c (mg/L)	Dose 1	Dose 2	Dose 3	Dose 4
12	0	0	0	0	0	0
13	1	0	0	0	0	0

| D8 | ▼ | ✕ | ✓ | ▦ | ≣ | =C6+C8 |

	A	B	C	D	E	F
1	Parameters					
2	Dose, d (mg)		1200			
3	Mass, m (kg)		41			
4	concentration, c0 (mg/L)		813	(=d/m/0.036)		
5	time constant, tau (hrs)		6.1			
6	dosing period, T (hrs)		12			
7	absorption time, t0 (hrs)		4			
8	time of dose		0	12	24	36
9	time of absorption		4	16	28	40

4. Fill to the right, all the way out to cell BZ8.

5. The equation in C9 (time of absorption) is correct, so fill to the right to cell BZ9.

6. Fill the columns C12:C112 to the right.

7. Redefine B12 to include all the C12:BZ12 in the sum. (See image above in upper right). Then fill down to B112.

8. Select the bottom row (A112:BZ112) and fill down to $t=200$ hrs.