Math Minute 9.1 What's the Right Dose?

One of the goals of pharmacogenomics is to find appropriate drugs and dosages for individuals of different genotypes. The hypothetical drug described in Figure 9.2 has minimal therapeutic effect on patients with *m/m* receptor genotypes, regardless of dose. However, patients with *wt/wt* or *wt/m* receptor genotypes can benefit from the drug, provided the dose is nontoxic. For concentrations greater than 50%, toxicity increases rapidly, while therapeutic effect increases very slowly. Therefore, drug concentration should probably be kept near 50% for all patients. Depending on factors such as disease severity, drug cost, and patient risk tolerance, lower concentrations might be desirable.

Using the data in Figure 9.2 and a mathematical model of drug metabolism, you can determine an appropriate dose for each drug metabolism genotype to achieve 50% peak concentration. A rough model of drug concentration in the bloodstream is based on what happens to the administered drug dose in an interval of time, say one hour. (A finer-scale model of drug concentration can be built using differential equations, in which the time interval is infinitesimal.)

For example, suppose 100 mg of the drug is administered orally to a patient with *wt/wt* metabolism genotype. The drug is absorbed into the bloodstream at a constant rate of 16 mg per hour, causing an increase in overall concentration over the first several hours. In what follows, we simplistically assume that the 16 mg enters the bloodstream all at once, at the beginning of the hour. We further assume that metabolizing proteins inactivate the drug at a rate proportional to the amount of active drug in the bloodstream at the beginning of the hour. Using an inactivation proportionality constant of 0.32, the following equations describe the amount of drug in the stomach at the end of hour n (S_n) and the amount of active drug in the bloodstream at the end of hour n (B_n):

$$S_{n+1} = \max(S_n - 16, 0)$$
$$B_{n+1} = (B_n + S_n - S_{n+1}) - 0.32 \times (B_n + S_n - S_{n+1}),$$

where the initial value of B is 0, and the initial value of S is 100. In the second equation, the quantity in parentheses is the amount of drug in the bloodstream at the beginning of hour $n + 1$, since B_n is the amount still active at the end of hour n and $S_n - S_{n+1}$ is the amount absorbed into the bloodstream at the beginning of hour $n + 1$. Thus, the second equation says that the amount of active drug in the bloodstream at the end of an hour is the amount at the beginning of the hour, minus 32% of that amount. The equation can be simplified algebraically by factoring out the quantity in parentheses. By entering these equations into a spreadsheet program or graphing calculator, you can verify that they generate the drug concentration curve for the *wt/wt* drug metabolism genotype (see Figure 9.2).

MATH MINUTE DISCOVERY QUESTIONS

1. Open the file drugmodel.xls in a spreadsheet program. The equations for the *wt/wt* drug metabolism model are implemented in this file. Using the same 16 mg/hr absorption rate, find an inactivation proportionality constant that generates the drug concentration curve for the *wt/m* metabolism genotype (see Figure 9.2).

2. Using the inactivation proportionality constant you found in Math Minute Discovery Question 1, adjust the initial dose down from 100 until the peak concentration is roughly 50%. This dosage would be more appropriate for patients with the *wt/m* metabolism genotype.

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1. Open the file drugmodel.xls in a spreadsheet program. The equations for the *wt/wt* drug metabolism model are implemented in this file. Using the same 16 mg/hr absorption rate, find an inactivation proportionality constant that generates the drug concentration curve for the *wt/m* metabolism genotype (see Figure 9.2b).

The first sheet in the file (labeled *wt/wt* model) is set up with an inactivation proportionality constant of 0.32, which produces the drug concentration curve for the *wt/wt* metabolism genotype (Figure 9.2a). The second sheet, labeled *wt/m* model, is set up for experimentation to answer this Discovery Question. The "Inactivation" constant, cell B3, is left blank (causing the formulas to use a value of 0). To produce the drug concentration curve for the *wt/m* metabolism genotype (Figure 9.2b), change the value in cell B3 to 0.11. Although the question does not ask students to repeat the process for the *m/m* metabolism genotype, the third sheet in the file is set up for this exploration.

2. Using the inactivation proportionality constant you found in Math Minute Discovery Question 1, adjust the initial dose down from 100 until the peak concentration is roughly 50%. This dosage would be more appropriate for patients with the *wt/m* metabolism genotype.

The initial dose is the amount found in the stomach at time 0 (cell D4). Change the value in cell D4 to 72 to achieve a peak concentration of about 50% (at time 5).