Determining the Proper Drug Dosage

When you take a pain-reliever to reduce the effects of a sore knee, you have many choices, each with a particular amount of active ingredient to be taken at specific intervals.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Size of Tablet</th>
<th>Repeat Every</th>
<th>Max Daily Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>325 mg</td>
<td>4-6 hours</td>
<td>10 in 24 hours</td>
</tr>
<tr>
<td>Aspirin</td>
<td>325 mg</td>
<td>4 hours</td>
<td>12 in 24 hours</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>200 mg</td>
<td>4-6 hours</td>
<td>6 in 24 hours</td>
</tr>
<tr>
<td>Naproxen Sodium</td>
<td>220 mg</td>
<td>12 hours</td>
<td>5 in 24 hours</td>
</tr>
</tbody>
</table>

Why those sizes and time intervals. How is the size of a pill determined?

The size and intervals are determined to meet two essential criteria: 1) the dosage is high enough to provide the needed pain relief, and 2) the dosage is not so high as to become toxic when taken regularly according to the prescribed timetable. The two important concentrations are the minimum effective concentration (MEC) and the minimum toxic concentration (MTC). Between these two limits lies the therapeutic window containing the range of concentrations for which the drug is effective and safe.

Determining the Dosage and Time Interval

A patient is given a dosage $Q$ mg/ml of a drug at regular intervals of time $T$ hours. Assume that the drug enters the system immediately upon ingestion and that the decrease in the concentration in the blood over time is proportional to the concentration itself with decay rate $k$. If a residual level above $H$ is unsafe ($H$ is the MTC) and below $L$ is ineffective ($L$ is the MEC), find a dose schedule $T$ for a safe and effective concentration of the drug in the blood.

$a)$ If the first dose is administered at $t = 0$, find the amount remaining in the blood at time $T$. This is known as the residual, $R_1$.

$b)$ Find $R_2$, $R_3$, and the $n$th residual $R_n$.

$c)$ Find the limiting value $R = \lim_{n \to \infty} R_n$ of the residual concentration for dose of size $Q$ mg/ml repeated at intervals of $T$ hours.

$d)$ If a residual level above $H$ is unsafe and below $L$ is ineffective, find a dose schedule $T$ for a safe and effective concentration of the drug in the blood.

$e)$ If the concentration must stay between $L$ and $H$, what is the appropriate dosage for this drug?

$f)$ Ibuprofen follows this model well. The dose is 200 mg every 6 hours. In the 6 hour time period, the body has metabolized about 50% of the drug in the body. Use this information to find $R$ for this dosage of ibuprofen.
g) From the table above, estimate the values of MEC, MTC, and \( k \) for aspirin, ibuprofen, naproxen sodium, and Acetaminophen.

h) Proscribe a therapeutic regimen (dosage and time interval) that is effective and safe for a drug with \( \text{MEC} = 320 \text{ mg/ml} \), \( \text{MTC} = 500 \text{ mg/ml} \), and which is eliminated at a constant rate of 12\% per hour. To be safe and to account for the variation in individual size and metabolic rates, you want to stay in the middle of the therapeutic region, so you design your dosage and intervals to be 15\% above MEC and 20\% below MTC.

What’s Going on in There?

A few years ago, I began taking two Aggrenox each day, one in the morning and one in the evening approximately 12 hours apart. Aggrenox is a combination of two drugs, 20 mg of Aspirin and 200 mg of Dipyridamole. These two drugs do not interact, so the pharmacokinetics in combination are the same as when each is administered in isolation. I presently weigh 188 pounds and have approximately 60 milliliters of blood per kilogram body weight

a) Use the pharmacokinetic information below to develop a model using Euler’s method that will allow you to describe the concentration in \( \mu \text{g/mL} \) of these two drugs in my body at any time until the process reaches its steady state. Initially, assume the drugs are instantly absorbed and available. You will need to use an if/then statement to allow for the pulse of medication followed by the exponential decay until the next dose. Once you are satisfied with this model, modify it to include the linear absorption. Compare the two models. Is much lost by assuming instantaneous absorption?

b) What happens to the concentration of each drug if I forget to take a pill one evening? If I miss a pill in the morning, should I take one or two in the evening?

b) What is the average value of the daily concentration once steady state has been reached?

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong>: Peak levels of aspirin are achieved 0.63 hours after ingestion. Aspirin is 99% metabolized to salicylate and other metabolites. At low doses, the elimination is first-order and the half-life remains constant at 2-3 hours; however, at higher doses, the enzymes responsible for metabolism become saturated and the apparent half-life can increase to 15-30 hours. Because of this, 5-7 days may be required before a steady-state concentration is reached. Salicylate and its metabolites are excreted primarily by the kidneys. Almost all of an ingested dose is excreted in the urine.</td>
</tr>
<tr>
<td><strong>Dipyridamole</strong>: Peak plasma levels of dipyridamole are achieved 2 hours after administration. Dipyridamole is metabolized in the liver and has a prolonged elimination phase, which, when administered in pill form, is first order and results in a half-life of about 13.6 hours. In geriatric patients (over 65), plasma concentrations (as determined as AUC) were about 40% higher than in younger subjects. <strong>Source</strong>: <a href="http://www.aggrenox.com/bipi/PageIndex">http://www.aggrenox.com/bipi/PageIndex</a></td>
</tr>
</tbody>
</table>
**Continuous Infusion**

One of the standard glucose tolerance tests infuses glucose continuously into the bloodstream at the rate of $G$ mg/min. Blood concentrations are measured at subsequent time intervals until steady state is reached. It is assumed that the glucose is used by the body according to the differential equation

$$\frac{dx}{dt} = -kx + G,$$

where $x$ is the amount of glucose, $G$ is the constant infusion rate of glucose, and $k$ is the “turnover rate”.

a) Explain the relationship between the turnover rate and the equilibrium solution.

b) Data from a typical glucose tolerance test are given below. Use the data to estimate the constants in the model and determine the concentration at steady state.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>x(t) (mg/dl)</td>
<td>85.0</td>
<td>105.4</td>
<td>120.1</td>
<td>127.3</td>
<td>131.9</td>
<td>134.4</td>
</tr>
</tbody>
</table>

**Convolution Integral**

In modeling the concentration of a medication that is introduced into the body over a period of time or the concentration of a hormone in the human body which has a similar infusion rate, simple models like the differential equation

$$\frac{dC}{dt} = -\alpha C(t) + S(t)$$

are often used. In this model, $C(t)$ is the concentration of the medication or hormone at time $t$ (which is being metabolized at a rate, $\alpha > 0$, proportional to the concentration at that time), while $S(t)$ is the rate at which the medication is being introduced or the hormone is being secreted into the system.

The two processes, secretion and elimination happen simultaneously. Of course, when $S(t) = 0$ we have the classic exponential decay model, $\frac{dC}{dt} = -\alpha C(t)$.

A more sophisticated model for the concentration is the convolution integral,

$$C(t) = \int_{-\infty}^{t} S(x) E(t - x) dx,$$

where $S$ is the rate of secretion and $E$ the rate of elimination. For most hormone secretions, $S(t)$ is either a pulse function or a variant of a Gaussian function (shown above). Note that $x$ is just a dummy variable in the integration; both $S$ and $E$ are functions of time.
1) Use technology to sketch a graph of the concentration function \( C(t) = \int_{-\infty}^{t} e^{-2x^2} e^{-0.6(t-x)} \, dx \).

Compare the graph to that of secretion function \( S(t) = e^{-2t^2} \).

2) For the integral model, \( C(t) = \int_{-\infty}^{t} S(x) E(t-x) \, dx \), find \( C(t) \) if \( E(t) = e^{-\alpha t} \) and \( S(t) = S \) (constant). Does the differential equation \( \frac{dC}{dt} = -\alpha C(t) + S(t) \) also represent this model?

3) Suppose \( C(t) = \int_{-\infty}^{t} S(x)e^{-\alpha(t-x)} \, dx \), with \( S(t) \) a non-constant secretion rate.

By using the definition of derivative, l’Hopital’s rule, and the 2nd Fundamental Theorem of Calculus, find \( \frac{dC}{dt} \).

   a) First, show that \( \frac{C(t+h) - C(t)}{h} = \frac{(e^{-\alpha h} - 1)C(t)}{h} + \frac{e^{-\alpha h}S(t+h)}{h} \int_{t}^{t+h} S(x)e^{-\alpha(t-x)} \, dx \).

   c) Find \( \lim_{h \to 0} \frac{C(t+h) - C(t)}{h} \).

The Origins of the Convolution Integral

How is the convolution integral created? Where did it come from?

Suppose you are required to take 4 pills 8 hours apart. Each pill contains 100 mg of medication and in the 8 hours, 5% of the medication is metabolized each hour. Define a continuous function of time whose value at time \( t \) is the amount of medication in your body \( t \) hours after taking the first pill. For simplicity, we assume instantaneous absorption.

We can define such a function in many ways. The most basic comes from our earlier work. Let example, \( A_1 = \begin{cases} 0 & \text{if } t < 0 \\ 100e^{-0.05t} & \text{if } t \geq 0 \end{cases} \) represents the function for the first 8 hour period. The second 8 hour period can be models with \( A_2 = \begin{cases} 0 & \text{if } t < 8 \\ (100 + 100e^{-4})^{-0.05t} & \text{if } t \geq 8 \end{cases} \) and the third by \( A_3 = \begin{cases} 0 & \text{if } t < 16 \\ (100 + 100e^{-0.4} + 100e^{-0.8})e^{-0.05t} & \text{if } t \geq 16 \end{cases} \), and the fourth by
Our function, then, is the very awkward function, 
\[ F(t) = A_1(t) + A_2(t) + A_3(t) + A_4(t) \]
with the graph shown at right.

But we can do much better than this.

Define 
\[ A(t) = \begin{cases} 
0 & \text{if } t < 0 \\
100e^{-0.05t} & \text{if } t \geq 0 
\end{cases} \]
then 
\[ F(t) = A(t) + A(t-8) + A(t-16) + A(t-24) \].

More compactly still, we can write 
\[ F(t) = \sum_{n=0}^{3} 100 \cdot A(t-8n) \].

Now, suppose instead of individual spikes of medication every 8 hours, the medication was delivered continuously over an extended interval of time. For example, suppose 180 mg of medication was administered according the function

\[ D(t) = \begin{cases} 
0 & \text{if } t < 0 \lor t > 6 \\
60 - |20t - 60| & \text{if } 0 \leq t \leq 6 
\end{cases} \]

We can approximate this process using the same method as before. Suppose we compute values of \( D \) for \( t = 0, 1, 2, 3, 4, 5, 6 \).

We can create an approximation using these values. We can assume the value of \( D \) is constant over the interval of width one, so

\[ F(t) = \sum_{n=0}^{6} D(t) \cdot A(t-n) \cdot \Delta t \text{ with } \Delta t = 1 \].

The graph is shown at below at left. We can generally make a better approximation using a smaller interval as shown at right below. As the size of the interval shrinks to zero, the curve smooths out.
\[ F(t) = \sum_{n=0}^{6} D(n\Delta t) A(t - n\Delta t) \cdot \Delta t \quad \text{with} \quad \Delta t = 1. \]

\[ F(t) = \sum_{n=0}^{12} D(n\Delta t) A(t - n\Delta t) \cdot \Delta t \quad \text{with} \quad \Delta t = \frac{1}{2}. \]

If we continue to shrink the size of the interval \( \Delta t \) and increase the number of intervals to cover the interval \([0,6] \), we can create the convolution integral \( C(t) = \int_{0}^{t} D(s) f(t - s) \, ds \). The convolution is graphed against the two approximations below.