ESTIMATION OF ELIMINATION HALF-LIFE FROM URINE DATA

Consider the urine data in Table B-1, obtained following a 50-mg i.v. bolus dose of a drug. These are the same data as presented in Table 3-1. The observations are times of urine collection, volumes collected, and concentrations of unchanged drug in each sample. These data are treated to derive further information. Of special interest are rate-time profile and cumulative amount excreted. The amount excreted in each time interval is the product of volume of urine collected and concentration, e.g., the amount in Sample 1 is 120 mL times 133 µg/mL or 16 mg; therefore, the average rate of excretion over the first 2-hr period is 8 mg/hr. The cumulative amount excreted up to any time is the sum of all drug excreted up to that time. By 24 hr, the cumulative amount excreted is 39.1 mg, and since 37.2 mg was excreted in the first 12 hr and only another 1.9 mg over the next 12 hr, 39.1 mg approximates the ultimate amount of drug excreted.

Excretion rate data are occasionally displayed as a bar histogram, but this form of presentation is not as useful as one in which the rate data are plotted against the midpoint of the collection interval on semilogarithmic paper (Fig. B-1). The time for the excretion rate to fall in half (e.g., from 5 mg/hr to 2.5 mg/hr) is the elimination half-life of the drug (2.8 hr). The reason for using midpoint time was given in Chap. 3, namely, the measured urinary excretion rate reflects the average plasma concentration during the collection interval.

Formal proof of the observation of elimination half-life is not difficult to derive. Using Eq. 21 of Chap. 3,

\[ \text{Excretion rate} = Cl_r \cdot C \]

If Dose \( \cdot e^{-kt} \) is substituted for \( C \),

<table>
<thead>
<tr>
<th>Sample</th>
<th>Time of Collection (hr)</th>
<th>Volume of Urine (mL)</th>
<th>Concentration of Unchanged Drug in Urine (µg/mL)</th>
<th>Amount Excreted in Interval (mg)</th>
<th>Excretion Rate (mg/hr)</th>
<th>Cumulative Amount Excreted (mg)</th>
<th>Amount Remaining to be Excreted (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>1</td>
<td>0-2</td>
<td>120</td>
<td>133</td>
<td>16.0</td>
<td>8</td>
<td>16.0</td>
<td>23.1</td>
</tr>
<tr>
<td>2</td>
<td>2-4</td>
<td>180</td>
<td>50</td>
<td>9.0</td>
<td>4.5</td>
<td>16.0</td>
<td>25.0</td>
</tr>
<tr>
<td>3</td>
<td>4-6</td>
<td>69</td>
<td>63</td>
<td>5.6</td>
<td>2.8</td>
<td>15.4</td>
<td>30.6</td>
</tr>
<tr>
<td>4</td>
<td>6-8</td>
<td>340</td>
<td>10</td>
<td>3.4</td>
<td>1.7</td>
<td>11.0</td>
<td>34.0</td>
</tr>
<tr>
<td>5</td>
<td>8-12</td>
<td>178</td>
<td>18</td>
<td>3.2</td>
<td>0.8</td>
<td>7.8</td>
<td>37.2</td>
</tr>
<tr>
<td>6</td>
<td>12-24</td>
<td>950</td>
<td>2</td>
<td>1.9</td>
<td>0.16</td>
<td>0.2</td>
<td>39.1</td>
</tr>
</tbody>
</table>
Excretion rate = \( \frac{C_l \cdot Dose}{V} \cdot e^{-kt} \)

and taking logarithms

\[
\ln(\text{excretion rate}) = \ln \left( \frac{C_l \cdot Dose}{V} \right) - k \cdot t
\]

The slope of the curve is \(-k\), the rate constant for elimination of drug by all routes. Even if renal excretion were only a small fraction of total drug elimination, the excretion rate would still decline with time in parallel with concentration. Concentration is the driving force for renal excretion; as concentration declines, so does rate of excretion.

In practice, uncertainty of complete bladder emptying and need to collect urine over short intervals, relative to the elimination half-life of the drug, pose limitations on the quality of excretion rate data. When complete urine recovery of drug is ensured, estimates of elimination half-life and elimination rate constant can also be made by analyzing cumulative excretion data. The cumulative excretion plots (Fig. B–2) generally tend to be smoother than the corresponding excretion rate plots.

The cumulative amount excreted up to any time \( t \), \( A(t) \), is obtained by summing the amount excreted unchanged in each time interval up to that time. For example, by 8 hr,

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**Fig. B–1.** Semilogarithmic plot of the rate of excretion against the midpoint time of urine collection. The period over which the average excretion rate was obtained is superimposed. Data from Table B–1.

**Fig. B–2.** The amount of drug excreted unchanged in the urine accumulates asymptotically toward a limiting value, \( A_{eo} \), following an i.v. bolus dose. Half that limiting amount is excreted in one half-life.
34.0 mg have been excreted. Initially, large amounts are excreted, but as the amount of
drug in the body falls, so does the excretion rate; by 24 hr, a limiting amount (39.1 mg)
has been excreted (Fig. B-2). Small amounts continue to be excreted beyond 24 hr, since
theoretically the amount of drug in the body approaches but never falls to zero. However,
these additional amounts do not substantially alter the 24 hr value. Accordingly, 39.1 mg
can be taken to be an estimate of the total amount of drug to be excreted unchanged ($Ae_\infty$).
Half this amount (approximately 20 mg) is excreted by 2.6 hr (Fig. B-2). Interestingly,
again, this is the value for the half-life of this drug, estimated from plasma concentration
and urinary excretion rate data. As the following analysis shows, this is more than a mere
coincidence.

The rate of excretion at any time is given by

$$\frac{dAe}{dt} = Cl_r \cdot C$$

The amount excreted up to time $t$ is obtained by integrating the rate equation.

$$Ae[\theta] = Cl_r \int_0^\theta C \cdot dt$$

Since the drug was given as an i.v. bolus, $C = \frac{Dose}{V} \cdot e^{-kt}$, so that

$$Ae[\theta] = \frac{Cl_r}{V} \int_0^\theta \frac{Dose}{V} \cdot e^{-kt} \cdot dt$$

or

$$Ae[\theta] = \frac{Cl_r}{V} \cdot \frac{Dose}{-k} \left[ e^{-kt} \right]_0$$

Remembering that $e^{-0} = 1$, the preceding equation reduces to

$$Ae[\theta] = \frac{Cl_r}{V \cdot k} \cdot \frac{Dose}{1 - e^{-kt}}$$

but since $e^{-\infty} = 0$, and $V \cdot k = CL$, the amount excreted by infinite time ($Ae_\infty$) must be
given by

$$Ae_\infty = \frac{Cl_r}{CL} \cdot \frac{Dose}{V \cdot k}$$

which when substituted into the preceding equation yields

$$Ae[\theta] = Ae_\infty \left( 1 - e^{-kt} \right)$$

Rearrangement of Eq. 10 gives
\[ Ae_{\infty} - Ae(t) = Ae_{\infty} \cdot e^{-kt} \]

and taking logarithms

\[ \ln(Ae_{\infty} - Ae(t)) = \ln Ae_{\infty} - k \cdot t \]

Thus, a semilogarithmic plot of \( Ae_{\infty} - Ae(t) \) against time should give a straight line with a slope of \(-k\).

As the difference, \( Ae_{\infty} - Ae(t) \), is the amount remaining to be excreted (ARE), the resulting plot is sometimes called an ARE plot. In practice, the value of ARE at each time is obtained by subtracting the cumulative amount excreted up to that time from the total amount excreted. These values are presented in the last column of Table B–1 and the corresponding semilogarithmic plot of ARE versus time is shown in Fig. B–3. The elimination half-life, taken as the time for the ARE to fall by one-half, is 2.8 hr. Hence, \( k = 0.25 \text{ hr}^{-1} \).

Several points should be noted. First, at zero time the value for ARE is \( Ae_{\infty} \). Second, the value of ARE is plotted against the actual time of urine collection, e.g., the time at which 5.1 mg remains to be excreted is 8 hr (Table B–1). In this last respect, the ARE plot has a distinct advantage over the excretion rate plot, in which the excretion rate is plotted against the midpoint of the urine collection interval. Recall that the use of the midpoint time was necessary because the excretion rate is an average value over the period of collection.

Although the ARE plot tends to smooth out the data, it is not used as frequently as the excretion rate plot for four reasons: (1) It requires an accurate estimate of \( Ae_{\infty} \), since an underestimation of \( Ae_{\infty} \) tends to grossly underestimate the true ARE values as \( Ae(t) \) approaches \( Ae_{\infty} \). This means that there has to be complete urine collection for at least four half-lives, which in clinical practice is often difficult to ensure. The rate method does not require urine to be collected until no more drug is excreted. (2) \( Ae(t) \) values are usually obtained by summing the amount excreted in each collection period. Hence, assay errors are accumulated, while failure to obtain a complete urine collection produces a systematic error in all subsequent estimates of \( Ae(t) \). The excretion rate analysis does not contain these
sources of error. (3) Smoothing out data can obscure important information. Urinary pH and urine flow fluctuate throughout the day. If the renal clearance of a drug is sensitive to these factors (Chap. 11), it is readily apparent in an excretion rate plot but tends to be lost in the ARE plot. (4) When the drug is administered extravascularly, e.g., orally, delays in excretion caused by absorption produce distortions of the ARE plot, frequently making analysis difficult. In contrast, the excretion rate plot can be readily analyzed.

**STUDY PROBLEMS**

1. Swintosky et al. (Sulfaethylthiadiazole II. Distribution and disappearance from the tissues following intravenous injection. J. Am. Pharm. Assoc., 46:403–411, 1957) studied the disposition kinetics of the sulfonamide, sulfaethylthiadiazole. Table B-2 contains a list of the amounts of drug excreted unchanged with time following an i.v. bolus dose of 2.0 g sulfaethylthiadiazole to a subject (weight 81 kg).

**Table B-2.**

<table>
<thead>
<tr>
<th>Time interval (hr)</th>
<th>0-3</th>
<th>3-6</th>
<th>6-9</th>
<th>9-12</th>
<th>12-15</th>
<th>15-24</th>
<th>24-48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount excreted unchanged (mg)</td>
<td>534</td>
<td>436</td>
<td>181</td>
<td>199</td>
<td>110</td>
<td>202</td>
<td>195</td>
</tr>
</tbody>
</table>

a. Estimate graphically the elimination half-life of sulfaethylthiadiazole from a semi-logarithmic plot of excretion rate against the midpoint time of urine collection.
b. Given that the cumulative amount excreted unchanged up to 48 hr represents a good estimate of $A_{e\text{cum}}$, calculate the fraction of the dose excreted unchanged.
c. Estimate the elimination half-life of sulfaethylthiadiazole from cumulative excretion data, and compare the answer with that obtained from the excretion rate data.

2. a. Suppose that the urine sample collected over the 3- to 6-hr interval in problem 1 was inadvertently discarded. Using both the excretion rate and ARE methods, determine the elimination half-life of the drug. Briefly discuss the problems encountered.
b. From the answers to problem 1, estimate how much unchanged drug in the body remains to be excreted at 48 hr.

Answers to Study Problems are in Appendix II, p. 576.