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Theory of the mean absorption time, an adjunct to conventional bioavailability studies

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The theory is outlined of a procedure for characterizing the time-course of drug absorption by determining the mean absorption time. The procedure requires data of the type normally collected in bioavailability studies.

In a recent paper it has been shown that the basic equations required to evaluate the extent of absorption of a drug can be derived using the methods of linear systems analysis, without recourse to a detailed model of drug disposition (Cutler, 1978a). With suitable data the time-course of absorption can be determined by means of numerical deconvolution (Cutler, 1978b, c). However, without a suitable reference input (such as an intravenous bolus dose) this method cannot be applied in practice. This paper outlines the theory of a procedure, applicable to a linear system, which characterizes the absorption rate by determining its mean absorption time; a merit of this procedure is that relative values can be obtained in cases where there is no suitable reference input which allows absolute values to be determined.

Theory

For a linear system the relationship between an input H(t) and the resulting response P(t) (e.g. the plasma or blood concentration of the drug, or the intensity of the pharmacological effect) can be written*

$$P(t) = \int_0^t F(T)H(t - T)\,dT$$

where F(t) denotes the response to a unit impulse input (Cutler, 1978a). On taking Laplace transforms, this equation becomes

$$p(s) = f(s)h(s) \quad .. \quad .. \quad (1)$$

where the lower case letters denote Laplace transforms of the functions denoted by the corresponding upper case letters. Differentiating with respect to s and rearranging,

$$\frac{1}{h(s)}\frac{dp}{ds} = \frac{f(s)}{h(s)}\frac{dh}{ds} + \frac{df}{ds}$$

Consider now two comparable inputs, which are distinguished by subscripts '1' and '2'; for each input an equation such as the above is obtained. Taking the difference between these equations, noting that f(s) is the same in both, we have

$$\frac{1}{h_1(s)}\frac{dp_1}{ds} - \frac{1}{h_2(s)}\frac{dp_2}{ds} = f(s)\left[\frac{1}{h_1(s)}\frac{dh_1}{ds} - \frac{1}{h_2(s)}\frac{dh_2}{ds}\right] \quad (2)$$

From equation 1,

$$f(s) = p_1(s)/h_1(s) = p_2(s)/h_2(s)$$

Eliminating f(s) from equation 2, and rearranging,

$$\frac{1}{p_1(s)}\frac{dp_1}{ds} - \frac{1}{p_2(s)}\frac{dp_2}{ds} = \frac{1}{h_1(s)}\frac{dh_1}{ds} - \frac{1}{h_2(s)}\frac{dh_2}{ds} \quad (3)$$

On transformation to the time domain, this equation yields the required relationship. The transformation is achieved using the following properties of the Laplace transform, for an arbitrary function X(t) with Laplace transform x(s).

$$\lim_{s\to 0}\{x(s)\} = \int_0^\infty X(t)\,dt$$

$$-\lim_{s\to 0}\left\{\frac{dx}{ds}\right\} = \int_0^\infty tX(t)\,dt$$

Equation 3 gives

$$\overline{H_2^0} - \overline{H_1^0} = \frac{\overline{P_2}}{A_2} - \frac{\overline{P_1}}{A_1} \quad .. (5)$$

where

$$A_i = \int_0^\infty P_i(t)\,dt \qquad i = 1, 2$$

* This equation requires that the system itself must be linear, but the restriction of linearity does not extend to the input function H(t) which may represent non-linear processes.

$$\bar{P}_i = \int_0^\infty tP_i(t)\,dt \qquad i = 1, 2$$

$$\bar{H}_i^0 = \int_0^\infty tH_i(t)\,dt \Big/ \int_0^\infty H_i(t)\,dt \quad i = 1, 2$$

The terms A_i and $\bar{P}_i$ are readily evaluated from experimental data; the former by numerical integration of the response $P_i(t)$ and the latter by numerical integration of the product $tP_i(t)$.

The terms $\bar{H}_i^0$ are the mean absorption times of the inputs $H_i(t)$. If the absorption of an individual molecule is regarded as a random event the absorption rate $H_i(t)$ can be regarded as specifying the probability distribution function for the absorption of an individual molecule. For this interpretation it is necessary to normalize $H_i(t)$ by dividing by the absorbed dose

$$D_i = \int_0^\infty H_i(t)\,dt \quad i = 1, 2$$

Then, $H_i(t)\,dt/D_i$ denotes the probability that an individual molecule, which is ultimately absorbed, is absorbed during the time interval $(t, t + dt)$. The mean absorption times $\bar{H}_i^0$ are the mean values of the probability distributions $H_i(t)/D_i$.

The molecules of the drug will remain at the input site for various periods of time before being absorbed; the mean absorption time is the mean time which a molecule spends at the input site before being absorbed. Rescigno & Segre (1966) have defined the mean transit time for a compartment in a similar way.

Further appreciation of the significance of the mean absorption time can be obtained from a consideration of specific absorption mechanisms. If the absorption process is first order,

$$H(t) = k_a D\, e^{-kat}$$

with D the absorbed dose and k_a a first order rate constant. The mean absorption time is

$$\bar{H}^0 = 1/k_a$$

which is proportional to the half-time of the absorption process ($\bar{H}^0$ = half-time/ln 2); alternatively, $\bar{H}^0$ can be identified as the time required for the fraction 1/e (~37%) of the dose to be absorbed.

If a competing first-order process occurs at the absorption site, with rate constant k_e,

$$H(t) = k_a D\, e^{-(ka+ke)t}$$

and the mean absorption time is

$$\bar{H}^0 = 1/(k_a + k_e)$$

which is again proportional to the absorption half-time.

If the input term H(t) arises from a dissolution process which follows the cube-root dissolution law (Cutler, 1978b),

$$H(t) = \frac{3D}{t_{dis}}(1 - t/t_{dis})^2 \quad t \leqslant t_{dis}$$

$$= 0 \qquad\qquad t > t_{dis}$$

The constant t_{dis} is the time required for complete dissolution. The mean absorption time in this case is

$$\bar{H}^0 = t_{dis}/4$$

This is the time required for approximately 42% of the dose to be absorbed (fraction absorbed = $(3/4)^3$).

As these examples show, the mean absorption time may be interpreted in terms of the parameters describing a proposed absorption mechanism. This is not the case with the 'time required to reach peak concentration', which can be regarded as an alternative measure of absorption rate. An explicit expression for this parameter (when one is available) will always include parameters describing the disposition of the drug. A simple interpretation of its significance in terms of an absorption mechanism is therefore not possible.

Division of $\bar{P}_i$ by A_i is also a normalizing procedure and it is notationally consistent to write equation 5 as

$$\bar{H}_2^0 - \bar{H}_1^0 = \bar{P}_2^0 - \bar{P}_1^0 \qquad (6)$$

where

$$\bar{P}_i^0 = \bar{P}_i/A_i \quad i = 1, 2.$$

Applications

(i) *Calculation of absolute values of the mean absorption time:* if an input is available such that $\bar{H}_1^0$ is known, the value of $\bar{H}_2^0$ can be found from equation 6 when $\bar{P}_1^0$ and $\bar{P}_2^0$ are evaluated from experimental data on $P_1(t)$ and $P_2(t)$. A situation in which $\bar{H}_1^0$ is known is when the input $H_1(t)$ is an impulse input. In this case $\bar{H}_1^0 = 0$. For example, if $H_1(t)$ represents a rapid intravenous injection and $H_2(t)$ represents the rate at which the drug enters the blood following an intramuscular injection, the

mean absorption time for the latter input is given by equation 6 to be

$$\bar{H}_2^0 = \bar{P}_2^0 - \bar{P}_1^0$$

(ii) *Ranking of inputs using relative values of the mean absorption time:* in the absence of a suitable reference input equation 6 allows ranking of different inputs in terms of their mean absorption times. This would be useful, for example, in comparing different oral dosage forms; this could be regarded as an adjunct to conventional bioavailability studies since equation 6 uses only data normally obtained in such studies.

(iii) *Analysis of two-step processes:* suppose that $H_1(t)$ represents the absorption rate following a unit dose of drug administered orally as a solution, and that $H_2(t)$ represents the absorption rate following an oral dosage form, such as a tablet. With $H_r(t)$ denoting the rate of release of drug into the gut contents, it can be shown that $H_2(t)$ is given by the equation

$$H_2(t) = \int_0^t H_r(t - T)H_1(T)\,dT$$

(Cutler, 1978a); this equation is based on the assumption that, once released, drug arising from the dosage form is subject to the same influences as the drug administered in solution. By following a procedure similar to that used to derive equation 5, it can be shown that

$$\bar{H}_2^0 = \bar{H}_1^0 + \bar{H}_r^0 \qquad (7)$$

where

$$\bar{H}_r^0 = \int_0^\infty tH_r(t)\,dt \Big/ \int_0^\infty H_r(t)\,dt$$

is the mean (normalized) release time of drug from the dosage form. Combining equations 6 and 7, we obtain

$$\bar{H}_r^0 = \bar{P}_2^0 - \bar{P}_1^0$$

Thus, the mean release time of the drug from the dosage form can be determined, in ignorance of both $\bar{H}_1^0$ and $\bar{H}_2^0$. The essential feature of this example is that $H_2(t)$ represents a two-step process, one step of which is represented by $H_1(t)$.

Example

A sample calculation, which is an example of application (i), has been performed using simulated data. The data were obtained using a unit impulse response given by $F(t) = A\exp(-at) + B\exp(-bt)$, with $A = B = b = 1$ and $a = 5$. The first-order input function $H(t) = kD\exp(-kt)$ was used, with $k = 4$, $D = 2$. The response P(t) which arises due to the input H(t) is given by

$$P(t) = \frac{kDA}{k-a}\left(e^{-at} - e^{-kt}\right) + \frac{kDB}{k-b}\left(e^{-bt} - e^{-kt}\right)$$

The data were obtained by evaluating the expressions for F(t) and P(t) at predetermined values of time, to give the following data. (t_i, F_i): (0, 2); (0·1, 1·51); (0·2, 1·19); (0·4, 0·81); (0·6, 0·60); (0·8, 0·47); (1·0, 0·37); (1·5, 0·22); (2·0, 0·14); (2·5. 0·08); (3·0, 0·05); (3·5, 0·03); (4·0, 0·02).

(t_i, P_i); (0, 0); (0·1, 1·14); (0·2, 1·64); (0·4, 1·78); (0·6, 1·55); (0·8, 1·27); (1·0, 1·02); (1·5, 0·60); (2·0, 0·36); (2·5, 0·22); (3·0, 0·13); (3·5, 0·08); (4·0, 0·05).

The t_i denotes the preselected time values, $F_i = F(t_i)$ and $P_i = P(t_i)$. The values for F_i and P_i have been rounded to two decimal places.

Using these data, evaluating the integrals involved by the trapezium method, equation 6 gives the mean absorption time as 0·24 (time units); the exact value (1/k) is 0·25 (time units).

The best method of evaluating the integrals involved in equation 6 will depend on the data. In some cases it will be necessary to use an extrapolation procedure to estimate the contribution to the integrals of the unmeasured response following the last data point. An alternative procedure to numerical integration is to fit the data to an empirical function which can be integrated analytically.

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