Approximation in Point–Area Deconvolution Algorithm as Mathematical Basis of Empirical Instantaneous Midpoint–Input Deconvolution Method

Keyphrases □ Point–area deconvolution algorithm—compared with instantaneous midpoint–input deconvolution method, drug absorption, calculation for *in vivo* drug input functions □ Drug absorption—point–area deconvolution algorithm compared with instantaneous midpoint–input deconvolution method □ Pharmacokinetics—point–area deconvolution algorithm compared with instantaneous midpoint–input deconvolution method, calculation for *in vivo* drug input functions

To the Editor:

Recently, Chiou (1) presented an empirically based deconvolution method for the determination of *in vivo* drug absorption, without reference to the point–area deconvolution algorithm (2). However, this empirical algorithm is equivalent to the point–area method when the analytical integration of the characteristic response is approximated by a rectangular function. Such an approximation to a defined integral can result in an unstable algorithm.

In the present communication, the relationship between the empirical method of Chiou (1) and the point–area deconvolution method (2) is derived, and the instability of the former method is demonstrated.

Define the plasma drug concentration–time function, $G(t)$, obtained after a unit drug impulse input (*e.g.*, intravenous bolus or oral solution) as the characteristic response of the body. Assume the body acts as a time-invariant linear system to drug input. Under the latter assumption, the plasma drug concentration–time function, $R(t)$, obtained after some arbitrary drug input, $In(t)$, into the body is defined by the convolution of the input function and the characteristic response. Thus, given $R(t)$ and $G(t)$, the input function, $In(t)$, can be defined by deconvolution of:

$$R(t) = \int_0^t In(t-\tau)G(t)\,d\tau \qquad \text{(Eq. 1)}$$

However, if $R(t)$ is sampled only at a set of time points $p_i (i \in 0, 1, 2, \ldots, p_0 = 0, p_{i+1} > p_i, p_i \geq 0)$, the analytical function $R(t)$ is not defined. The deconvolution of $R(p_i)$ and $G(t)$ to obtain $In(t)$ is an ill-defined problem since the convolution of a number of input functions with $G(t)$ will generate the observed responses, $R(p_i)$. Consequently, deconvolution must be based on some logical algorithm that assumes some functional form for either $R(t)$ or the input function (2–5). In particular, a staircase input function can always be derived such that the convolution of this function with $G(t)$ generates the observed responses, $R(p_i)$. The latter is the point–area deconvolution method (2).

For a staircase input function into a time-invariant linear system, the responses, $R(p_i)$, are given by:

$$R(p_i) = \sum_{j=1}^{i}\left[K_j \int_{p_i-p_j}^{p_i-p_{j-1}} G(t)\,dt\right] \qquad i \in 0, 1, 2, \ldots \qquad \text{(Eq. 2)}$$

where $R(p_0) = 0$, $K_0 = 0$, and K_i $(i \in 1, 2, \ldots)$ is the magnitude of a step of duration $(p_i - p_{i-1})$ in the staircase input function. The cumulative input in any interval, $(p_i - p_{i-1})$, is $K_i(p_i - p_{i-1})$, which is given by Eq. 2 as:

$$K_i(p_i - p_{i-1}) = \frac{\left[R(p_i) - \sum_{j=1}^{i-1}\left(K_j \int_{p_i-p_j}^{p_i-p_{j-1}} G(t)\,dt\right)\right](p_i - p_{i-1})}{\int_0^{p_i-p_{i-1}} G(t)\,dt} \qquad \text{(Eq. 3)}$$

If the integrals of $G(t)$ are approximated by rectangular functions centered about the midpoint of the integration interval, then:

$$\int_{p_i-p_j}^{p_i-p_{j-1}} G(t)\,dt \simeq (p_j - p_{j-1})G\left(p_i - \frac{p_j}{2} - \frac{p_{j-1}}{2}\right) \qquad \text{(Eq. 4)}$$

Using the approximations of Eq. 4 in Eq. 3 gives:

$$K_i(p_i - p_{i-1}) = \frac{R(p_i) - \sum_{j=1}^{i-1} K_j(p_j - p_{j-1})G\left(p_i - \frac{p_j}{2} - \frac{p_{j-1}}{2}\right)}{G\left(\frac{p_i - p_{i-1}}{2}\right)} \qquad \text{(Eq. 5)}$$

Substituting $f_j = K_j(p_j - p_{j-1})$ into Eq. 5 gives:

$$f_j = \frac{R(p_i) - \sum_{j=1}^{i-1} f_i G\left(p_i - \frac{p_j}{2} - \frac{p_{j-1}}{2}\right)}{G\left(\frac{p_i - p_{i-1}}{2}\right)} \qquad \text{(Eq. 6)}$$

where $f_i (i \in 1, 2, \ldots)$ is the fraction of the dose absorbed in the time interval $(p_i - p_{i-1})$, and $\Sigma_{j=1}^{i} f_j$ is the cumulative drug input at time point p_i.

The deconvolution algorithm specified by Eq. 6 is equivalent to the empirical algorithm specified by Chiou (1) and is simply an approximation to the point–area method (2). The point–area deconvolution method is a correction and rationalization of a convolution method described by Rescigno and Segre (6). In the latter algorithm, the integrals of $G(t)$ are approximated by rectangular functions centered about the midpoint of integration. Consequently, the new algorithm of Chiou (instantaneous midpoint–input method) is a restatement of a previously known algorithm.

Provided the approximations specified by Eq. 4 are reasonable, Eqs. 3 and 6 should give essentially similar results when applied to the determination of *in vivo* drug

Table I—Comparison of the Theoretical and Calculated Cumulative Drug Input for a Zero-Order Lidocaine Infusion

Hours	$R(t)$, μg/ml	Cumulative Drug Input, mg: Theoretical	Cumulative Drug Input, mg: Calculated by Instantaneous Midpoint–Input Method
0.5	0.8314	55.8	69.54 (24.62)[a]
1.0	1.1884	111.6	132.22 (18.48)
1.5	1.4720	167.4	192.74 (15.14)
2.0	1.7037	223.2	252.58 (13.16)
2.5	1.8929	279.0	312.21 (11.90)

[a] Number in parentheses is the percent deviation from the theoretical value.

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input. This is true for the examples involving exponential drug input functions cited by Chiou (Tables I–IV in Ref. 1). Since the point–area method defines a staircase input function, the method gives exact results for zero-order absorption rates. Consequently, the examples cited by Chiou for zero-order absorption (Tables VI and VII in Ref. 1) simply reflect the degree of accuracy of the approximations, specified by Eq. 4, for the particular characteristic responses used in the examples. When the approximations of Eq. 4 are invalid, the instantaneous midpoint–input method gives erroneous cumulative drug input functions. As an example, consider the plasma concentrations (micrograms per milliliter) of lidocaine after a 1-mg iv bolus as the characteristic response, where $G(t) = 0.0276e^{-0.123t} + 0.0084e^{-0.00673t}$ and the units of t are minutes.

Apply the instantaneous midpoint–input deconvolution method to the plasma drug concentrations that would result from a 1.86-mg/min constant intravenous infusion of lidocaine. The results of applying this method are given in Table I. This example illustrates the large errors that can result by approximating integrals by rectangular functions. The point–area method gives exact results for this example (Table I).

In conclusion, the instantaneous midpoint–input method is an approximation of the point–area method. The use of approximations in the latter method can result in large errors in the cumulative drug input functions, and such unnecessary approximations should be avoided.

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D. P. Vaughan

School of Pharmacy
Sunderland Polytechnic
Sunderland, Tyne and Wear
United Kingdom

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Stability of Nitroglycerin Ointment

Keyphrases □ Nitroglycerin—stability of ointment at elevated temperatures □ Vasodilators—stability of nitroglycerin ointment at elevated temperatures □ Stability—nitroglycerin ointment at elevated temperatures

To the Editor:

Topical nitroglycerin therapy offers a longer duration of action than sublingual administration and thus is popular as a prophylactic treatment for angina pectoris (1, 2). Previous studies indicated that the potency of nitroglycerin tablets may be affected by the environment in which the tablets are stored (3, 4). It also was demonstrated that nitroglycerin in solutions for intravenous use interacts with plastic infusion bags and intravenous giving sets (5, 6), resulting in decreased availability of nitroglycerin. Since we are unaware of any report on the stability of nitroglycerin ointment during storage, we evaluated the stability of nitroglycerin ointment capsules stored at elevated temperatures for extended periods.

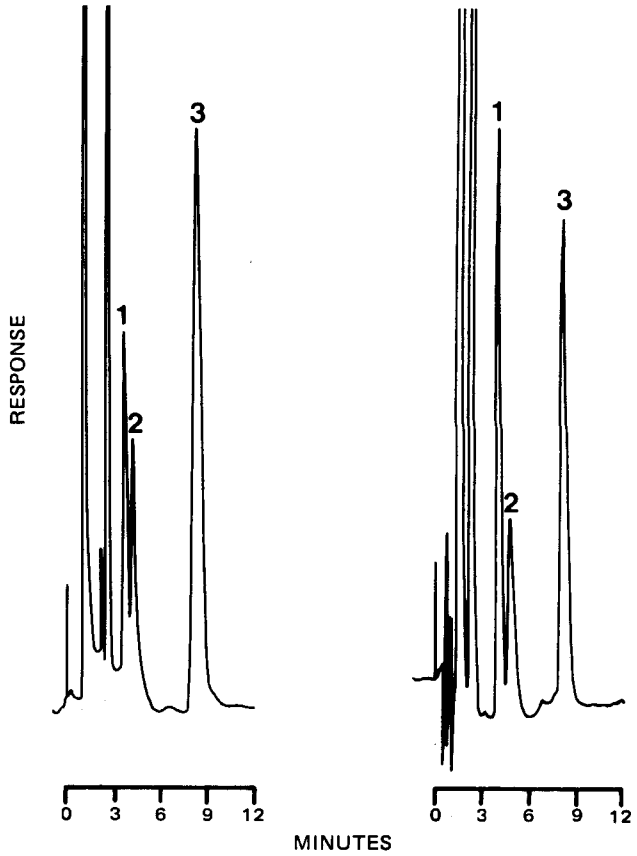

Figure 1—*(Left) Chromatogram of an aqueous solution of nitroglycerin and the two dinitroglycerins. Key: 1, 1,3-dinitroglycerin; 2, 1,2-dinitroglycerin; and 3, nitroglycerin. (Right) Chromatogram of an octanol extract of nitroglycerin ointment. Key: 1, unknown interfering peak; 2, unknown interfering peak; and 3, nitroglycerin.*

Capsules from unopened bottles of nitroglycerin (3% w/w) ointment capsules[1] were stored on individual glass dishes in an oven at 37 ± 1° and in the original glass bottle at room temperature (20–24°) in the dark. Capsules were removed from storage after 5, 10, and 18 weeks and were assayed for nitroglycerin content as follows. Each capsule was cut open, the ointment was removed completely, and its weight was recorded. The nitroglycerin then was extracted from the ointment by vortexing with 5 ml of octanol for 10 min and centrifuging at 3000 rpm for 10 min. This method achieved >96% extraction of nitroglycerin.

The extract then was diluted with methanol before assay using kinetic (7) and high-performance liquid chromatographic (HPLC) methods (8). Standard curves for the two methods were constructed by adding known amounts of nitroglycerin, standardized by the method of Dean and Baun (9), to octanol, which then was diluted in methanol to give appropriate concentrations for analysis. In four determinations of six different nitroglycerin concentra-

[1] Nitrolate, Roche Products, Sydney, Australia.

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