Europ.J.clin.Pharmacol. 10, 433-440 (1976)

General Derivation of the Ideal Intravenous Drug Input Required to Achieve and Maintain a Constant Plasma Drug Concentration. Theoretical Application to Lignocaine Therapy

D. P. Vaughan and G. T. Tucker

School of Pharmacy and Biology, Sunderland Polytechnic, and Academic Division of Medicine, Section of Therapeutics, The University of Sheffield, The Royal Infirmary, Sheffield, U.K.

Received: October 2, 1975, and in revised form: May 5, 1976, accepted: May 8, 1975

Summary. A constant plasma drug concentration can be achieved and maintained by the intravenous administration of an initial bolus loading dose in conjunction with a constant rate and an exponential intravenous drug infusion. The drug input required to achieve a constant plasma drug concentration is derived without making any assumptions about the nature of drug distribution within the body or elimination from the body.

Key words: Pharmacokinetics, drug input equations, constant plasma drug concentrations, lignocaine therapy of myocardial infarction.

Drug distribution within the body is often represented by a linear mammillary compartmental model with first-order drug transfer between compartments. Drug elimination is described by a first order elimination process from the central compartment. Utilising these concepts, Krüger-Thiemer (1968) derived the intravenous drug input necessary to achieve and maintain a constant plasma drug concentration. This input was expressed in terms of intercompartment drug transfer rate constants and the elimination constant. However, a linear mammilary model with elimination from the central compartment is not the only compartmental model applicable for describing plasma drug concentration - time curves. For example, drug elimination may be considered to occur from a peripheral compartment in addition to the central compartment (Vaughan and Beckett, 1974; Vaughan et al, 1975; Vaughan, 1975). Furthermore, drug disposition is increasingly being represented by so-called 'physiological' or 'perfusion' models (Price, 1960; Price et al, 1960; Bischoff et al, 1971). In view of the above and the realisation that drug disposition models are gross simplifications of the real system, it may be assumed that a drug input derived by defining a specific model is not generally applicable.

In this communication a general expression for an intravenous drug input which will result in a constant plasma drug concentration is derived without any recourse to hypothetical concepts of drug disposition.

THEORY AND DISCUSSION

Input and Response in Linear Systems

The relationship between an input function, $F_{in}(t)$, and the response, $F_{out}(t)$, for a linear system is defined by the convolution integral as:

$$F_{out}(t) = F_{in}(t) * F_{dis}(t) = \int_0^t F_{in}(\tau) \cdot F_{dis}(t-\tau)\,d\tau. \quad \ldots(1)$$

where $F_{dis}(t)$ is the response of the system to a unit impulse input. The latter

function is a characteristic of the system.

Provided the response of a linear system to either an impulse or step input can be determined, the responses to an arbitrary input can also be found. Conversely, the input required to achieve a particular response or output can be established.

When applying these latter principles to pharmacokinetics the body is regarded as the system and the time function describing plasma drug concentrations achieved with some arbitrary drug input is regarded as the system's response. In practice an impulse drug input is approximated by a rapidly administered intravenous drug bolus.

Often the time function describing plasma drug concentrations (C_p) obtained after a single intravenous bolus dose (D) can be represented by a summation of exponential functions, viz

$$C_p(t) = D\delta(t) * \sum_{i=1}^{N} A_i \; e^{-\alpha_i t}$$

$$\equiv D \sum_{i=1}^{N} A_i \cdot e^{-\alpha_i t} \qquad \ldots(2)$$

where A_i and α_i are real positive coefficients. By definition, α_i is greater than α_{i+1}. If the body behaves as a linear system the coefficients are constants independent of the dose (D), and the plasma drug concentrations are directly proportional to the intravenously administered drug dose.

The responses to a unit impulse is obtained directly from equation (2) as:

$$\text{Plasma drug concentrations obtained with a unit impulse drug dose} = \sum_{i=1}^{N} A_i \cdot e^{-\alpha_i t} = F_{dis}(t) \qquad \ldots(3)$$

When intravenous drug administration is a constant rate infusion, beginning at time t = 0, the plasma drug concentration - time function, $C_{pa}(t)$ is given by:

$$C_{pa}(t) = k_o H(t) * \sum_{i=1}^{N} A_i \cdot e^{-\alpha_i t} \qquad \ldots(4)$$

where H(t) is the unit step function and k_o is the infusion rate (units of mass time^{-1}). H(t) is usually taken as understood and omitted. For an intravenous drug dose of D which is administered at an exponential rate, defined by the rate constant k_a; the plasma concentration - time function, $C_{pb}(t)$, is given by:

$$C_{pb}(t) = k_a D e^{-k_a t} * \sum_{i=1}^{N} A_i \cdot e^{-\alpha_i t} \qquad \ldots(5)$$

The time function $De^{-k_a t}$ (see equation (5)) describes the amount of drug remaining to be infused and $k_a De^{-k_a t}$ is the appropriate input time function (i.e. $F_{in}(t)$).

Integration of $F_{in}(t)$ as used in equations (2), (4) and (5) with respect to time between the limits of t = 0 and t gives the amount of drug which has entered the body at time t.

Intravenous Drug Input Required to Achieve and Maintain a Constant Plasma Drug Concentration (C_{pss})

Immediately after a unit intravenous bolus drug dose (i.e. at t = 0) the plasma drug concentration is given by equation (3) as:

$$\text{plasma concentration at t = 0 after a unit intravenous dose} = \sum_{i=1}^{N} A_i \qquad \ldots(6)$$

Similarly, the intravenous dose D_1 required to achieve an initial plasma drug concentration of C_{pss} is given by:

$$D_1 = \frac{C_{pss}}{\sum_{i=1}^{N} A_i} \qquad \ldots(7)$$

Since after an intravenous dose of D_1 plasma drug concentrations are only equivalent to C_{pss} at time t = 0, some additional drug input is required if the plasma drug concentration is to be maintained at C_{pss} for all time (i.e. t = 0 to t = ∞). Achievement of a constant plasma drug concentration (C_{pss}) requires that:

$$C_{p1}(t) + C_{p2}(t) = \left[D_1\delta(t) * \sum_{i=1}^{N} A_i \cdot e^{-\alpha_i t} + F_{in1}(t) * \sum_{i=1}^{N} A_i \cdot e^{-\alpha_i t} \right] = \text{constant} = C_{pss} \qquad \ldots(8)$$

where $C_{p1}(t)$ and $C_{p2}(t)$ are the time functions describing plasma drug concentration obtained with an intravenous bolus dose of D_1 and an intravenous drug input of $F_{in1}(t)$, respectively. Consequently, an explicit expression for

$F_{in1}(t)$ is required to completely define an intravenous drug input that will result in a constant plasma drug concentration of C_{pss}.

To derive a general but explicit expression for $F_{in1}(t)$ it is convenient to Laplace transform equation (8) since this yields an algebraic expression:

$$\frac{C_{pss}}{s} = D_1 \sum_{i=1}^{N} \frac{A_i}{s+\alpha_i} + f_{in} \sum_{i=1}^{N} \frac{A_i}{s+\alpha_i} \qquad \ldots(9)$$

where s is the Laplace variable and f_{in} is the Laplace transform of $F_{in1}(t)$. An expression for f_{in}/s can be obtained by division of equation (9) by s and rearrangement thus,

$$\frac{f_{in}}{s} = \frac{C_{pss}}{s^2 \sum_{i=1}^{N} \frac{A_i}{(s+\alpha_i)}} - \left[\frac{D_1}{s}\right] \qquad \ldots(10)$$

Equation (10) can be further rearranged to:

$$\frac{f_{in}}{s} = \frac{C_{pss} \prod_{i=1}^{N} (s+\alpha_i)}{s^2 \sum_{i=1}^{N} \left(A_i \prod_{\substack{j=1 \\ j\neq i}}^{N} (s+\alpha_j) \right)} - \left[\frac{D_1}{s}\right] \qquad \ldots(11)$$

The denominator of the first right hand term in equation (11) can be expressed as a continuous function, viz

$$\frac{f_{in}}{s} = \frac{C_{pss} \prod_{i=1}^{N} (s+\alpha_i)}{s^2 \prod_{i=1}^{N-1} b_i \cdot \prod_{i=1}^{N-1} (s+c_i)} - \left[\frac{D_1}{s}\right] \qquad \ldots(12)$$

where the b's and c's are defined by N simultaneous equations in terms of the A's and α's. These N simultaneous equations are obtained by equating the denominators of the first terms in equations (11) and (12), whence:

$$\sum_{i=1}^{N} \left[A_i \prod_{\substack{j=1 \\ j\neq i}}^{N} (s+\alpha_j) \right] = \prod_{i=1}^{N-1} b_i \cdot \prod_{i=1}^{N-1} (s+c_i) \qquad \ldots(13)$$

Expansion of both sides of equation (13) and subsequently equating the coefficients of like powers of s on both sides yields these N simultaneous equations. One of these N equations is always given by:

$$\prod_{i=1}^{N-1} b_i = \sum_{i=1}^{N} A_i \qquad \ldots(14)$$

Since the integration of a function, F(τ), which possesses an image function, f(s), from 0 to a variable point t corresponds to the division of the image function by s (Doetsch, 1961) then f_{in}/s in equations (10), (11) and (12) is the Laplace transform of the integral $F_{in1}(t)$. Defining f_{in}/s as q than inverse transformation of equation (12) will yield a time function Q(t) which upon differentiation with respect to time gives the desired function $F_{in}(t)$.

Inverse Transformation of Equation (12)

The degree of s in the denominator of equation (12) is greater than the degree of s in the numerator. Consequently, equation (12) can be expanded into a finite series of partial fractions which can be inversely transformed term by term. The partial expansion of equation (12) is given by:

$$q = \frac{C_{pss}}{\prod_{i=1}^{N-1} b_i} \left[\frac{R}{s^2} + \frac{T}{s} + \sum_{i=1}^{N-1} \frac{U_i}{(s+c_i)} \right] - \left[\frac{D_1}{s}\right] \qquad \ldots(15)$$

The terms R, T and U in equation (15) are defined by the following general equations:

$$R = \frac{\prod_{i=1}^{N} \alpha_i}{\prod_{i=1}^{N-1} c_i} \qquad \ldots(16)$$

$$T = \frac{\sum_{i=1}^{N} \left[\prod_{\substack{j=1 \\ j\neq i}}^{N} \alpha_j \right]}{\prod_{i=1}^{N-1} c_i} - \frac{\prod_{i=1}^{N} \alpha_i \left[\sum_{i=1}^{N-1} \left(\prod_{\substack{j=1 \\ j\neq i}}^{N-1} c_j \right) \right]}{\prod_{i=1}^{N-1} c_i^2} \qquad \ldots(17)$$

$$U_i = \frac{\prod_{j=1}^{N} (\alpha_j - c_i)}{c_i^2 \prod_{\substack{j=1 \\ j\neq i}}^{N-1} (c_j - c_i)} \qquad (i=1 \text{ to } N-1) \qquad \ldots(18)$$

Inverse transformation of equation (15) gives Q(t) as:

$$Q(t) = \frac{C_{pss}}{\prod_{i=1}^{N-1} b_1}\left[Rt + T + \sum_{i=1}^{N-1} U_i \cdot e^{-c_i t}\right] - D_1 \quad \ldots(19)$$

Differentiation of equation (19) with respect to time yields:

$$F_{in1}(t) = \frac{C_{pss}}{\prod_{i=1}^{N-1} b_i}\left[R - \sum_{i=1}^{N-1} c_i U_i \cdot e^{-c_i t}\right]$$

$$= D_1 \cdot \left[R - \sum_{i=1}^{N-1} c_i U_i \cdot e^{-c_i t}\right] \quad \ldots(20)$$

The equivalence $D_1 = C_{pss} \Big/ \prod_{i=1}^{N-1} b_i$ is obtained by combining equations (7) and (14).

It should be emphasised that the general function, $F_{in1}(t)$, represented by equation (20) is that function which when integrated with respect to time between limits of t = 0 and t gives the total amount of drug infused into the body at time t. By reference to equations (4) and (5), the input function given by equation (20) is described as a constant rate intravenous infusion of rate D_1R and N-1 exponential intravenous infusions. The exponential infusion can be physically represented as N-1 drug reservoirs, each with an initial drug amount of $-D_1 U_i$ ($i = 1$ to $N-1$) from which drug is delivered into a vein in such a manner that the drug in each reservoir decreases exponentially from its initial value at a rate of c_i. When the intravenous drug input defined by equation (20) is administered in conjunction with an intravenous bolus dose of D_1 (see equation (8)) a constant plasma drug concentration of C_{pss} will result provided the drug infusion (equation (20)) is continued.

To achieve a constant plasma drug concentration of C_{pss} from t = 0 to t = ∞ using a specific drug whose disposition function is known (i.e. the number of exponentials N and the coefficients A_i and α_i have been established) requires the evaluation of the initial loading dose (D_1) which is evaluated by the application of equation (7) and the evaluation of the infusion defined by equation (20). The calculations involved in evaluating the appropriate form of equation (20) when N=2 and N=3 are given below.

Evaluation of R, U_i and c_i for N=2 and N=3

1) *for N=2*

Applying equation (13) when N=2, then:

$$A_1(s+\alpha_2) + A_2(s+\alpha_1) = b_1(s+c_1) \quad \ldots(21)$$

Expanding both sides of equation (21) and equating the coefficients of like powers in s gives:

$$A_1 + A_2 = b_1$$

$$A_1\alpha_2 + A_2\alpha_1 = b_1c_1 \quad \ldots(22)$$

c_1 is obtained by solving the above simultaneous equations and is given by:

$$c_1 = \frac{A_1\,\alpha_2 + A_2\,\alpha_1}{A_1 + A_2} \quad \ldots(23)$$

Substitution of c_1 (equation (23)) into equation (16) gives R as:

$$R = \frac{\alpha_1\alpha_2}{c_1} = \frac{\alpha_1\alpha_2\,(A_1+A_2)}{A_1\alpha_2 + A_2\alpha_1} \quad \ldots(24)$$

The value of $-U_1$ is obtained by applying equation (18) and can be expressed in terms of the constant coefficients by substitution of c_1, whence:

$$-U_1 = \frac{-(\alpha_1-c_1)(\alpha_2-c_1)}{c_1^2} = \frac{A_1A_2(\alpha_2^2+\alpha_1^2-2\alpha_1\alpha_2)}{(A_1\alpha_2 + A_2\alpha_1)^2} \quad \ldots(25)$$

Since A_1, A_2, and α_2 are real positive numbers, $-U_1$ is positive provided $\alpha_1^2 + \alpha_2^2$ is greater than $2\alpha_1\alpha_2$. The latter is true for all real nonequivalent positive values of α_1 and α_2.

2) *For N=3*

Applying equation (13) when N=3 then:

$$A_1(s+\alpha_2)(s+\alpha_3) + A_2(s+\alpha_1)(s+\alpha_3) + A_3(s+\alpha_1)(s+\alpha_2) = b_1b_2(s+c_1)(s+c_2) \quad \ldots(26)$$

Expanding both sides of equation (26) and equating the coefficients of the powers in s gives:

$$A_1 + A_2 + A_3 = b_1b_2 \quad \ldots(27a)$$

$$A_1(\alpha_1+\alpha_2) + A_2(\alpha_1+\alpha_3) + A_3(\alpha_1+\alpha_2) = b_1b_2(c_1+c_2) \quad \ldots(27b)$$

$$A_1\alpha_2\alpha_3 + A_2\alpha_1\alpha_2 + A_3\alpha_1\alpha_2 = b_1b_2c_1c_2 \quad \ldots(27c)$$

Solving equations (27a) and (27c) for c_1c_2 and substitution into the appropriate form of equation (16) gives R as:

$$R = \frac{\alpha_1\alpha_2\alpha_3}{c_1c_2} = \frac{\alpha_1\alpha_2\alpha_3\ (A_1+A_2+A_3)}{A_1\alpha_2\alpha_3+A_2\alpha_1\alpha_3+A_3\alpha_1\alpha_2} \quad \ldots(28)$$

c_1 and c_2 can be evaluated by rearranging equations (27a) and (27c) to give a quadratic equation and subsequent solution. Using this procedure, c_1 and c_2 are evaluated as:

$$c_1 = \frac{1}{2}\ (g + \sqrt{g^2 - 4h}\ ) \quad \ldots(29)$$

$$c_2 = \frac{1}{2}\ (g - \sqrt{g^2 - 4h}\ ) \quad \ldots(30)$$

where:

$$g = \frac{A_1(\alpha_2+\alpha_3) + A_2(\alpha_1+\alpha_3) + A_3(\alpha_1+\alpha_2)}{A_1 + A_2 + A_3}$$

$$h = \frac{A_1\alpha_2\alpha_3 + A_2\alpha_1\alpha_3 + A_3\alpha_1\alpha_2}{A_1 + A_2 + A_3}$$

Both c_1 and c_2 are real positive numbers and c_1 is greater than c_2. By applying equation (18), $-U_1$ and $-U_2$ are given as:

$$-U_1 = \frac{-(\alpha_1-c_1)(\alpha_2-c_1)(\alpha_3-c_1)}{c_1^2\ (c_2-c_1)} \quad \ldots(31a)$$

$$-U_2 = \frac{-(\alpha_1-c_2)(\alpha_2-c_2)(\alpha_3-c_2)}{c_2^2\ (c_1-c_2)} \quad \ldots(31b)$$

For a drug with a disposition function described by a four exponential equation requires the evaluation of c_1, c_2 and c_3. These values can be obtained by applying a cubic solution to the N (N=4) simultaneous equations which relate the A_i's and α_i's to the c_i's and b_i's. However, with the magnitudes of α_1, α_2, α_3 and α_4 likely to be encountered, inaccurate estimates of c_1, c_2 and c_3 can be obtained because of the insensitivity of the cosine tablets. In such cases a digital computer should be used for the cubic solution, which also avoids the generally turgid algebra associated with the general cubic solution.

Administration of an intravenous infusion defined by equation (20) in conjunction with a bolus intravenous injection (defined by equation (7)) will achieve a constant plasma drug concentration for all time (i.e. t = 0 to t = ∞) for any drug whose plasma drug concentration-time curve, after a bolus intravenous dose, is described by a summation of exponential functions. A necessary restriction to the validity of the above derivation is that the principle of superposition applies. Concepts concerning the nature of drug disposition within the body are not required for the derivation. Consequently, the derived input is generally applicable.

The dosage flow, D(t), derived by Krüger-Thiemer (1968) for a linear mammillary pharmacokinetic model with elimination of drug from the central compartment is analogous to $F_{in1}(t)$, see equation (20), derived in this text.

Intravenous drug inputs that differ from the simultaneous administration of an intravenous drug bolus, a constant rate infusion and N-1 exponential infusions cannot produce an exact plasma drug concentration. However, since the coefficients A_i and α_i (1=1 to N) are obtained from experimental observations, the calculated drug input is subject to statistical error and plasma drug concentrations obtained with this input can deviate from the predicted constant value of C_{pss}. Nevertheless, this latter consideration also applies to all other types of intravenous drug administration.

Potential Application of the Derived Drug Input

Lignocaine is frequently administered as a bolus intravenous dose of 1 - 2 mg/kg accompanied by a constant intravenous infusion of 1 - 4 mg/min to control ventricular dysrhythmias associated with myocardial infarction. However, its value as an effective drug remains controversial (Bennett et al, 1971; Adgey et al, 1971; Darby et al, 1972).

Clinical response to lignocaine therapy has been correlated with blood levels (Gianelly et al, 1967; Jewitt et al, 1968) and the drug has a narrow therapeutic index. Blood concentrations of 1.2 to 5.5 µg/ml are considered to be the limits of the therapeutic range (Gianelly et al, 1967; Foldes et al, 1960; Bellet et al, 1971). Since most deaths occur during the first few hours following onset of myocardial infarction (McNeilly and Pemberton, 1968; Bondurant, 1969) it would seem essential to achieve and maintain a therapeutic blood concentration of lignocaine as early as possible during treatment. A possible explanation of the reported inefficacy of lignocaine is that the various rates of drug administration do not maintain therapeutic blood concentration in the critical first few hours.

Pharmacokinetic analysis of lignocaine blood concentrations demonstrate conclusively that a single bolus and a constant rate intravenous infusion cannot maintain

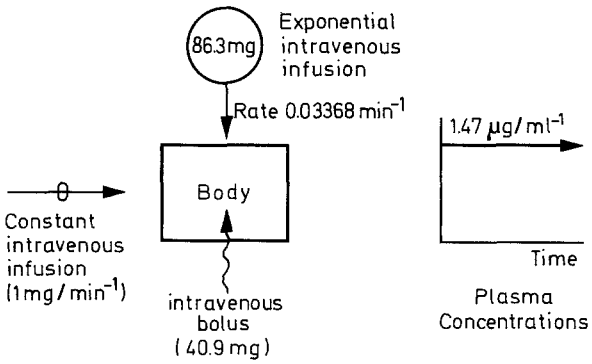

Fig. 1. Intravenous drug inputs required to achieve and maintain a constant plasma lignocaine concentration of 1.47 µg ml^{-1}

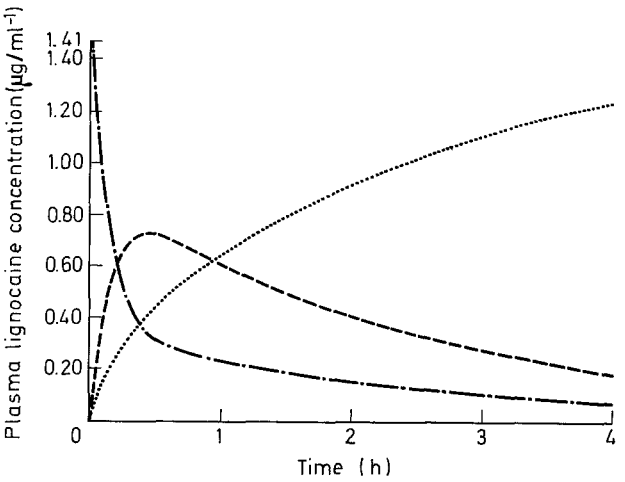

Fig. 2. Plasma lignocaine concentrations obtained with the individual drug inputs defined in figure 1. Intravenous bolus (—•—); constant rate infusion (····) and exponential infusion (---)

blood levels in the therapeutic range during the first few hours of drug administration (Shen and Gibaldi, 1974; Rowland et al, 1971; Vaughan, Tucker and Lord, unpublished observations). Recent clinical data (Aps et al, 1976) corroborate the latter deductions.

To illustrate the potential application of the derived equations an ideal input is now calculated using lignocaine as the example. Rowland and associates (1971) describe the disposition kinetics of lignocaine in normal subjects as a biexponential function. The average parameters established by the latter authors are used to calculate the ideal drug input to achieve and maintain a constant plasma concentration of lignocaine.

A mean disposition function for lignocaine is given by equation (32), calculated from Rowland et al, 1971:
mean disposition for lignocaine (i.e. plasma concentration for a unit impulse drug input of 1 mg of lignocaine)

$$= 0.0276 \cdot e^{-0.123t} + 0.0084 \cdot e^{-0.00673t} \quad \ldots(32)$$

whence

$$A_1 = 0.0276 \text{ µg ml}^{-1}, \quad A_2 = 0.084 \text{ µg ml}^{-1}$$

and

$$\alpha_1 = 0.123 \text{ min}^{-1}, \quad \alpha_2 = 0.00673 \text{ min}^{-1} \quad \ldots(33)$$

Defining the desired plasma concentration of lignocaine as 1.47 µg ml^{-1} the ideal drug input to achieve and maintain this concentration for all time can be calculated as follows. To achieve an initial concentration of 1.47 µg ml at t = 0 requires a bolus injection of 40.9 mg (i.e. D_1 = 40.9 mg, see equations (7) and (32)). The magnitude of a constant rate intravenous infusion which if administered alone would eventually achieve a concentration of 1.47 µg ml^{-1} is given by D_1 R (see equation (20)) where R is defined by equation (24) (units of R = min^{-1}). Substitution of the values of A_1, A_2, α_1, and α_2 into equation (24), and multiplication by D_1 gives the constant intravenous infusion rate as 1 mg min^{-1}. The exponential infusion rate is obtained from equations (23) and (33) as 0.03386 min^{-1} and the initial dose in the exponential drug reservoir is given by $-U_1D_1$. Substitution of the values given by equation (33) into equation (25) and multiplication by D_1 gives the latter value, whence $-U_1D_1$ = 86.3 mg.

The totaly of the latter inputs will achieve and maintain a constant plasma concentration of 1.47 µg ml^{-1}; these inputs are depicted in Figure 1 and the plasma concentrations achieved with each individual drug input is given in Figure 2.

In practice constant intravenous infusions are readily achieved using intravenous infusion pumps. However, exponential intravenous infusions require specifically-designed pump units. A number of authors have described programmable intravenous drug administration devices (Ake Oberg, 1970; Spoerel et al, 1970) and simple intravenous drip dilution methods are available for achieving exponential inputs (Boyes et al, 1970).

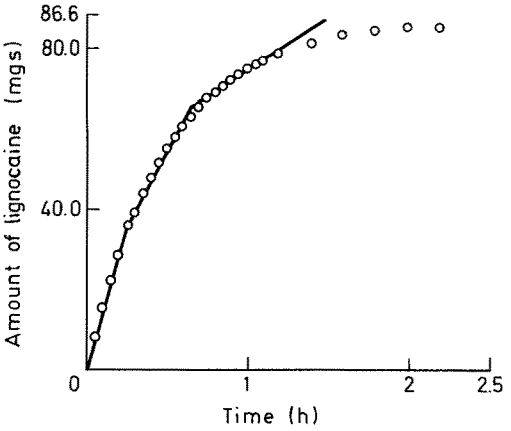

Fig. 3. The cumulative amount of lignocaine delivered by the exponential infusion and its piecewise description by three linear segments. Data points are calculated from equation (36) in the text

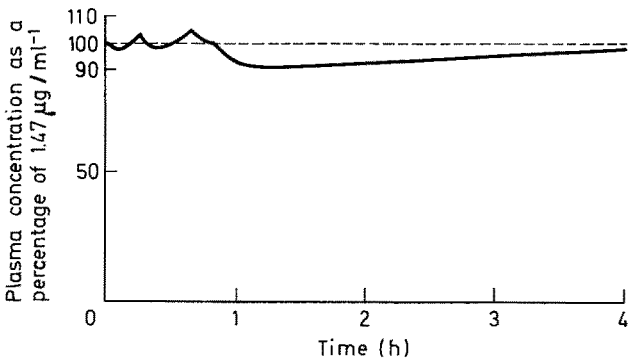

Fig. 4. Plasma concentration (——) of lignocaine obtained with a bolus drug dose and a stepped constant intravenous infusion. The dashed line represents the ideal lignocaine concentration of 1.47 μg ml^{-1}

Alternatively a step input can be used as an approximation to an exponential input. The latter method is now described within the context of the lignocaine example.

Approximation of Exponential Inputs by Step Inputs

The integral of an input function defines the cumulative drug input profile. Piecewise describing the cumulative input profile by linear segments then defines a series of constant rate infusions which will achieve a similar cumulative drug input. In the case of lignocaine the time course curve of drug in the exponential reservoir is given by:

$$-D_1U_1e^{-c_1t} = 86.6\,e^{-0.03386t} \quad \ldots(34)$$

and the appropriate input function is given by:

$$\text{Exponential input function} = c_1D_1U_1e^{-c_1t} \quad \ldots(35)$$

Integration of equation (35) with respect to time gives the cumulative amount of lignocaine absorbed into the body via the exponential mode, whence

$$\int_0^t -C_1D_1U_1e^{-C_1t}\,dt = -D_1U_1(1-e^{-c_1t}) = 86.6\ (1-e^{-0.03386t}) \quad \ldots(36)$$

The cumulative exponential input for lignocaine (calculated from equation (36)) is given in Figure 3. The latter curve has been approximated by three linear segments (see Fig. 3); the first segment (gradient 2.4 mg min^{-1}) approximates the curve from t = 0 to t = 15 min, the second segment (gradient 1.25 mg min^{-1}) from t = 15 to t = 39 min and the third segment (gradient 0.55 mg min^{-1}) approximates the curve from t = 39 to t = 87 min. Since the integration of a constant rate intravenous input function is linear the cumulative input described by the three segments represents a stepped intravenous input, i.e. constant rate intravenous infusion of rate 2.40 mg min^{-1} for 15 min which is abruptly decreased to a rate of 1.25 mg min^{-1} at t = 15 min, the latter constant rate infusion being maintained for another 24 minutes at which time the infusion rate is abruptly decreased to a rate of 0.55 mg min^{-1}, and at t = 87 min the constant intravenous infusion is discontinued. The latter step input is an approximation to an exponential drug input. Consequently the exponential and constant intravenous drug input (rate = 1 mg min^{-1}) which is required to maintain the lignocaine plasma concentration at 1.47 μg ml^{-1} can be approximated to by the use of constant infusion pumps with adjustable drives. The total plasma lignocaine concentrations obtained with the approximated exponential input, a bolus and a constant infusion of 1 mg are depicted in Figure 4. The plasma concentrations obtained using the step input function exhibit maximal deviation from the ideal of -8.6 and +5.0% which are close to the analytical accuracy for lignocaine determinations in plasma (C_a ±5%). In conclusion the control of plasma drug concentrations can be achieved by applying the equation derived in the text and acceptable control can be achieved by approximating

the required exponential inputs to stepped input functions. Recent attempts to control lignocaine plasma concentration using stepped input functions (Aps et al, 1976) demonstrate the practical validity of this approach.

Acknowledgements. We thank Miss S. Lord for developing computer programmes and generating the data used in figures 2, 3, and 4.

REFERENCES

Adgey, A.A.J., Geddes, J.J., Webb, S.W., Allen, J.D., James, R.G.G., Zaidi, S.A., Pantridge, J.F.: Acute phase of myocardial infarction. Lancet *1971 II*, 501-504

Aps, C., Bell, J.A., Jenkins, B.S., Poole-Wilson, P.A., Reynold, F.: Logical approach to lignocaine therapy. Brit. med. J. *1976 I*, 13-15

Bellet, S., Roman, L., Kostis, J.B., Fleischmann, D.: Intramuscular lidocaine in the therapy of ventricular arrhythmias. Amer. J. Cardiol. *27*, 291-293

Bennett, M.A., Wilner, J.M., Pentecost, B.L.: Controlled trial of lignocaine in the prophylaxis of ventricular arrhythmias complicating myocardial infaction. Lancet *1970 II*, 909-911

Bischoff, K.D., Dedrick, R.L., Zahorko, D.S., Longstreth, J.A.: Methotrexate pharmacokinetics. J. pharm. Sci. *60*, 1128-1133 (1971)

Boundurant, S.: Problems of the pre-hospital phase of acute myocardial infarction. Amer. J. Cardiol. *24*, 612-161 (1969)

Boyes, R., Adams, M., Duce, B.R.: Oral absorbtion kinetics of lidocaine hydrochloride in dogs. J. Pharmacol. Exp. Ther. *174*, 174-178 (1970)

Darby, S., Bennett, M.A., Cruickshand, J.C., Pentecost, B.L.: Trial of combined intramuscular and intravenous lignocaine in prophylaxis of ventricular tachyarrhythmias. Lancet *1972 I*, 817-819

Foldes, F.F., Molloy, R., McNall, P.G., Koukal, L.R.: Comparison of the toxicity of intravenously given local anaesthetic agents in man. J. Amer. med. Ass. *172*, 1493-1498 (1960)

Gianelly, R., von der Groeben, J.O., Spivack, A. P., Harrison, D.C.: Effect of lidocaine on ventricular arrhythmias in patients with coronary heart disease. New Engl. J. Med. *277*, 1215-1219 (1967)

Jewitt, D.W., Kishon, Y., Thomas, M.: Lignocaine in the management of arrhythmias after acute myocardial infarction. Lancet *1968 I*, 266-270

Krüger-Thiemer, E.: Continuous intravenous infusion and multicompartment accumulation. Europ. J. Pharmacol *4*, 317-324 (1968)

McNeilly, R.H., Pemberton, J.: Duration of last attack in 998 fatal cases of coronary artery disease and its relation to possible cardiac resucitation. Brit. med. J. *1968 III*, 139-142

Price, H.L.: A dynamic concept of the distribution of thiopental in the human body. Anaesthesiology *21*, 40-45 (1960)

Price, H.L., Kovnat, P.J., Safer, B.S., Conner, E.H., Price, M.L.: The uptake of thiopental by body tissue and its relation to the duration of narcosis. Clin. Pharmacol. Ther. *1*, 16-22 (1960)

Rowland, M., Thomson, P.D., Guichard, A.G., Melmon, K.L.: Disposition kinetics of lidocaine in normal subjects. Annals. N.Y. Acad. Sci. *179*, 383-398 (1971)

Shen, D., Gibaldi, M.: A hypothesis for the rapid attainment and maintenance of lidocaine plasma levels. J. clin. Pharmacol. *14*, 339-344 (1974)

Spoerel, W.E., Thomas, A., Gerula, G.R.: Continuous epidural analgesia. Experience with mechanical injection devices. Canad. Anaesth. Soc. J. *17*, 37-51 (1970)

Vaughan, D.P.: Estimation of biological availability after oral drug administration when the drug is eliminated by urinary excretion and metabolism. J. Pharm. Pharmacol. *27*, 458-461 (1975)

Vaughan, D.P., Beckett, A.H.: An analysis of the inter-subject variation in the metabolism of pentazocine. J. Pharm. Pharmacol. *26*, 789-798 (1974)

Vaughan, D.P., Mallard, D.J.H., Trainor, A., Mitchard, M.: General pharmacokinetic equations for linear mammillary models with drug absorption into peripheral compartments. Europ. J. clin. Pharmacol. *8*, 141-148 (1975)

Dr. D.P. Vaughan
School of Pharmacy and Biology
Sunderland Polytechnic
Sunderland, SR1 3SD
England