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A General Method for Calculating the Dosage Scheme in Linear Pharmacokinetics

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Summary. The problem of correctly administering drugs is considered with respect to pharmacokinetics. A general method for calculating the dosage scheme for any linear model is presented, if the desired blood level or amount of drug in any other compartment is given.

Key words: linear system theory; linear pharmacokinetics, dosage regimen calculations, theoretical analysis

For optimal application of drugs several general factors must be taken into account. A major factor is the time course of drug concentrations in man, that is to say pharmacokinetics. The following work considers the dosage problem with respect to this aspect. In anaesthesiology, for instance, it is often desirable to have a short induction time to reach a desired anaesthetic state, which is then maintained for the duration of anaesthesia. For intravenously administered drugs this is often achieved by a loading dose, given as a quick infusion or an initial bolus, followed by a maintenance dose given at a lower, constant rate infusion (Wagner 1974), or by repetition of small boluses. These schemes have the advantage of being simple and easy to use, but they also have at least two disadvantages:

1. the pharmacokinetic data of the drug are taken into account only very roughly, especially in the induction phase,

2. the time course of drug concentration does not necessarily parallel the time course of the pharmacodynamic effect, e. g. the relationship between norepinephrine plasma levels and blood pressure (Segré 1968).

These difficulties can be circumvented if the infusion scheme is modelled in such a way as to achieve any desired time course of drug concentration, which, in turn, gives rise to the desired time course of the pharmacodynamic effect.

Theory

In the framework of compartment models the problem to solve is how to infuse into a compartment i to achieve a prescribed time course of amount of drug in compartment j. If this problem is confined to linear pharmacokinetics it can be solved exactly. To achieve a constant blood level from the very beginning onwards, Krüger-Thiemer (1968) calculated an infusion scheme for an open, linear, mamillary n-compartment model.

In the following a systematic procedure to calculate the infusion scheme will be exemplified for a two compartment model (Fig. 1). The solution for the general linear n-compartment model is given in the mathematical appendix A.

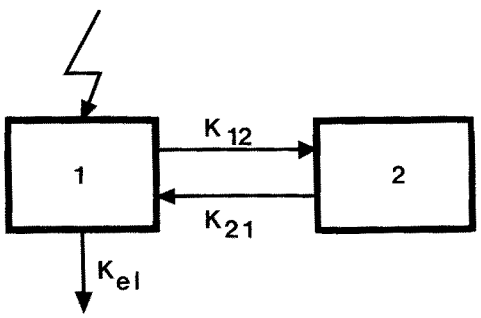

Fig. 1. A two compartment model

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Let $A_i(t)$ i = 1,2 denote the amount of drug in compartment i at time t. The model depicted in Fig. 1 is in general described by the following set of differential equations:

$$\frac{dA_1(t)}{dt} = -(k_{e1}+k_{12})A_1(t) + k_{21}A_2(t) \qquad (1.1a)$$

$$\frac{dA_2(t)}{dt} = k_{12}A_1(t) - k_{21}A_2(t) \qquad (1.1b)$$

The solution $G_i(t)$ i = 1,2 of the differential equations after the injection of a bolus of amount 1 at time t = 0 in compartment 1 is:

$$G_1(t) = \frac{1}{A+B}(Ae^{-\alpha t}+Be^{-\beta t}) \qquad (1.2a)$$

$$G_2(t) = \frac{k_{12}}{\alpha-\beta}(e^{-\beta t}-e^{-\alpha t}), \qquad (1.2b)$$

where α, β, A/(A+B), B/(A+B) are well known functions of the transfer constants k_{e1}, k_{12}, k_{21}. From a mathematical point of view, $G_i(t)$ can be interpreted as Green's function of the differential equations. They contain all the information about the pharmacokinetic model presented by Eqs. (1.1a, b).

The amount of drug $A_i(t)$ due to any application scheme I(t) is then given by the formula:

$$A_i(t) = \int_0^t dt' G_i(t-t')I(t') \quad i = 1,2 \qquad (1.3)$$

which reflects the superposition principle, which in turn relies on the linearity of Equations 1.1a, b.

Equation 1.3 is a fundamental equation in linear system theory. Interpreted in terms of linear pharmacokinetics, it relates the actual amount $A_i(t)$ in compartment i at time t to the application scheme I(t) and the pharmacokinetic model represented by $G_i(t)$. It is simple to do a computer simulation of $A_i(t)$, if $G_i(t)$ is known and the application scheme I(t) is arbitrarily given. Moreover this equation is model independent in the framework of linear pharmacokinetics. This means in practice that, if one measures the blood levels of a drug after bolus injection, the blood level can be computed which would be produced by any administration scheme, independent of the order or form of the linear model necessary to fit the blood levels. On the other hand, Eq. (1.3) may be the basis to calculate $G_i(t)$ and to determine the pharmacokinetic model, if $A_i(t)$ is measured and I(t) is known. This may be of interest in clinical research, because measurement of blood levels after any application, not just bolus injection, would be suitable for determination of the model. Technically, Eq. (1.3) has to be transformed into an inhomogeneous Volterra integral equation, which can be solved by iteration. Last but not least the application scheme I(t) can be calculated if the pharmacokinetic data are known and the amounts $A_1(t)$ or $A_2(t)$ are given. Laplace transformation of (1.3) transforms the integral equation into an algebraic equation. If the Laplace transforms of $A_i(t)$, $G_i(t)$, and I(t) are named $\bar{A}_i(p)$, $\bar{G}_i(p)$ and $\bar{I}(p)$, (1.3) can be written as

$$\bar{A}_i(p) = \bar{G}_i(p)\bar{I}(p) \quad i = 1,2. \qquad (1.4)$$

The solution of (1.4) for $\bar{I}(p)$ is trivial, the back transformation yields

$$I(t) = \frac{1}{2\pi i}\int_{-i\infty+s}^{+i\infty+s} dp\, e^{pt}\bar{A}_i(p)/\bar{G}_i(p) \qquad (1.5)$$

(s denotes an arbitrary small positive number).

The main problem that remains is evaluation of the integral expression on the right hand side of (1.5). It can most easily be solved by applying the theorem of residues of the theory of functions of a complex variable (Peschl, 1967; see also mathematical appendix B). Although the monographs of Wagner (1975) and Gibaldi and Perrier (1975) give a list of Laplace transformations of frequently used functions, it is not always sufficient for calculating dosage schemes, as the following four examples will show.

Examples

The values in this section were calculated for a model drug with the following kinetic data:

A = 0.9 µg/ml; B = 0.1 µg/ml; D = 20 mg
α = 0.25/min; β = 0.01/min.

As the simplest example we wish the desired blood level c(t) to be as depicted in Fig. 2a.

$$c(t) = \begin{cases} 0 \text{ for } t<0 \\ c_0 \text{ for } t\geqq 0 \end{cases} \qquad (2.1a)$$

or

$$A_1(t) = \begin{cases} 0 & \text{for } t<0 \\ \dfrac{c_0 D}{A+B} & \text{for } t\geqq 0 \end{cases} \qquad (2.1b)$$

The Laplace transforms $\bar{A}_1(p)$, $\bar{G}_1(p)$, and $\bar{G}_2(p)$ are given by

$$A_1(p) = \frac{c_o D}{A+B}\,\frac{1}{p},$$

$$\bar{G}_1(p) = \frac{1}{A+B}\left(\frac{A}{\alpha+p} + \frac{B}{\beta+p}\right),$$

$$\bar{G}_2(p) = \frac{k_{12}}{\alpha-\beta}\left(\frac{1}{\beta+p} - \frac{1}{\alpha+p}\right).$$

Hence we have

$$\bar{I}(p) = c_o D\,\frac{(\alpha+p)\,(\beta+p)}{(A(\beta+p)+B(\alpha+p))p} \tag{2.2}$$

or

$$I(t) = \frac{1}{2\pi i}\int_{-i\infty+s}^{+i\infty+s} dp\, e^{pt}\,\bar{I}(p) \tag{2.3}$$

$A_2(t)$ is given by

$$A_2(t) = \int_o^t dt'\, G_2(t-t')\, I(t')$$

$$= \frac{1}{2\pi i}\int_{-i\infty+s}^{+i\infty+s} dp\, e^{pt}\,\bar{G}_2(p)\,\bar{I}(p). \tag{2.4}$$

Evaluation of (2.3) according to the rules of Appendix B and of (2.4) results in

$$I(t) = \frac{Dc_o}{A+B}\left(\delta(t) + k_{e1} + k_{12}e^{-k_{21}t}\right) \tag{2.5}$$

$$A_2(t) = \frac{Dc_o}{A+B}\,\frac{k_{12}}{k_{21}}\left(1-e^{-k_{21}t}\right) \tag{2.6}$$

The symbol $\times\,\delta(t)$ means that a bolus of amount $\times$ has to be given at time $t = 0$. $I(t)$ and $A_2(t)$ are depicted in Figs. 2b and 2c. The different terms of (2.5) are readily interpreted. The bolus $Dc_o/(A+B)$ is required to produce a blood level c_o onwards from the very beginning, $k_{e1}\,Dc_o/(A+B)$ is the maintenance infusion rate and the last term is necessary to prevent the "dip" between the decreasing blood level after the bolus injection and the slowly increasing blood level produced by the maintenance rate infusion.

Another example suitable for a creeping dosage, or the study of threshold phenomena, has linearly rising blood level for a time t_1 (Fig. 3a).
This means

$$c(t) = \begin{cases} 0 & \text{for } t<0 \\ \dfrac{c_o}{t_1}\,t & \text{for } 0\leqq t\leqq t_1 \\ c_o & \text{for } t\geqslant t_1 \end{cases} \tag{3.1}$$

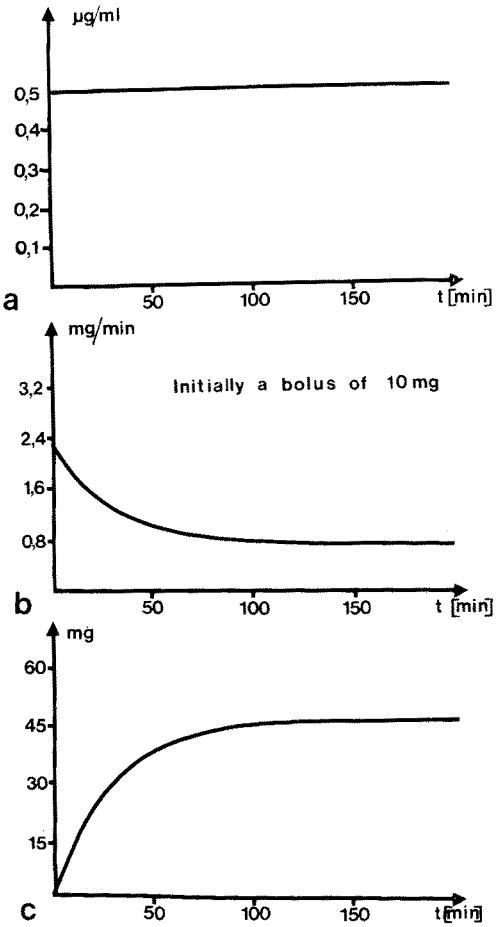

Fig. 2a–c. The desired blood level **a** is achieved using the infusion scheme **b**. The amount in the peripheral compartment behaves like **c**

$$\text{or } A_1(t) = \frac{D}{A+B}\,c(t).$$

$\bar{A}_1(p)$ is given by

$$\bar{A}_1(p) = \frac{Dc_o}{A+B}\,\frac{1-e^{-pt_1}}{t_1 p^2}. \tag{3.2}$$

$I(t)$ has to be calculated from

$$I(t) = \frac{Dc_o}{2\pi i}\int_{-i\infty+s}^{+i\infty+s} dp\, e^{pt} \times \frac{(\alpha+p)\,(\beta+p)\,(1-e^{-pt_1})}{(A(\beta+p)+B(\alpha+p))\,t_1 p^2}, \tag{3.3}$$

with the result $I(t) = \dfrac{Dc_o}{A+B} \times$

$$\begin{cases} \dfrac{1}{t_1} + \dfrac{k_{e1}\,t}{t_1} + \dfrac{k_{12}}{k_{21}t_1}\left(1-e^{-k_{21}t}\right) & \text{for } o \leqq t \leqq t_1 \\ k_{e1} + \dfrac{k_{12}}{k_{21}t_1}\left(e^{k_{21}t_1}-1\right)e^{-k_{21}t} & \text{for } t > t_1. \end{cases} \tag{3.4}$$

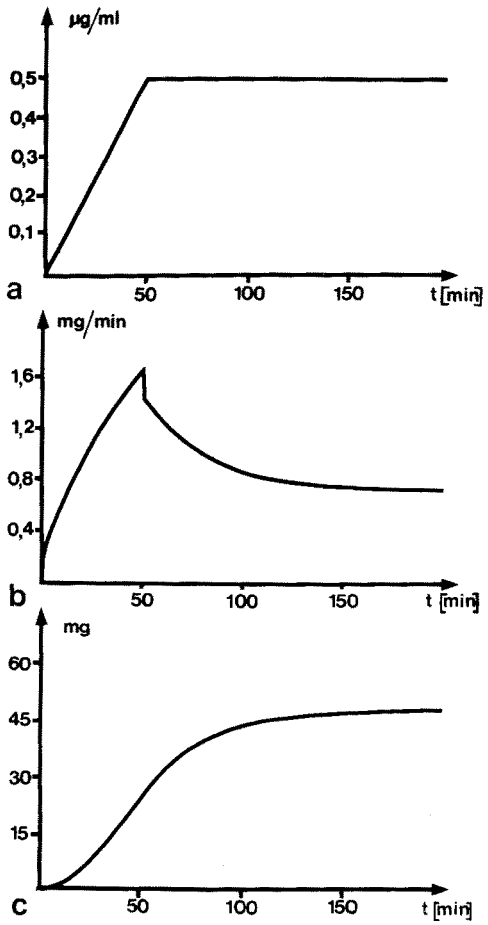

Fig. 3a–c. Linearly rising blood levels **a** require an infusion scheme like **b**, which gives rise to the amount of drug in the peripheral compartment as depicted in **c**

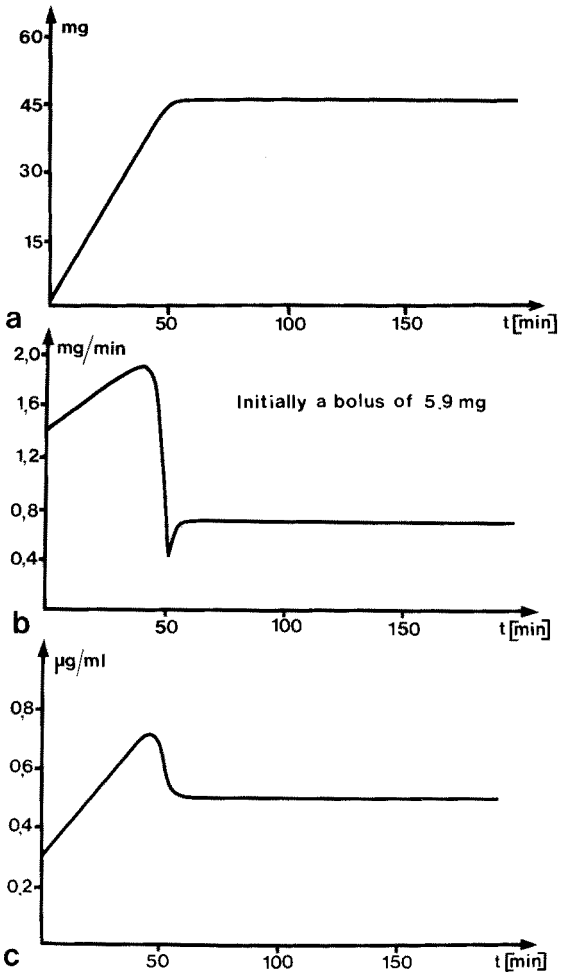

Fig. 4a–c. Linearly rising amounts of drug in the peripheral compartment **a** are achieved by the infusion scheme **b**. The resultant blood level behaves like **c**

It is remarkable that I(t) does not increase linearly with t at t=0, but that there is a base infusion at t=0; Figs. 3b and 3c show I(t) and $A_2(t)$. If the extent of the action of a drug has to be located in compartment 2, the question arises if a quantity of drug can be generated in compartment 2 by application of the drug to compartment 1, the time course of which equals the shape of the blood level curves just mentioned. For the first example this can immediately be denied, because there a certain time is always required for the distribution from "1" to "2". For the second example, too, this must also be denied, as calculation shows. But, both cases may be approximated by a desired amount $A_2(t)$ of (Fig. 4a)

$$A_2(t) = M + \frac{M}{2}\frac{(t-t')}{t_1} - \frac{M}{2}\left(\frac{(t-t')^2}{t_1^2} + \frac{d}{t_1^2}\right)^{1/2} \tag{4.1}$$

Making d very small one may approximate the function

$$A_2^0(t) = \begin{cases} 0 & \text{for } t<0 \\ \dfrac{M}{t_1}\,t & \text{for } 0 \leqq t \leqq t_1 \\ M & \text{for } t>t_1 \end{cases}$$

as closely as is desired. By making t_1 very small the steady-state amount M can be reached as quickly as is wished. Since $A_2(0)$ must be zero, t′ is fixed as

$$t' = \frac{t_1^2 - d}{t_1}.$$

Now the equation

$$A_2(t) = \int_0^t dt'\, G_2(t-t')\, I(t')$$

has to be solved.
The Laplace transform $\tilde{A}_2(p)$ of $A_2(t)$ is calculated as

$$\bar{A}_2(p) = M\left\{\frac{1-\frac{t'}{2t_1}}{p} + \frac{1}{2p^2t_1} - \frac{1}{2t_1}e^{-pt'} \int_{-t'}^{\infty} d\tau\, e^{-p\tau}\sqrt{\tau^2+d}\right\} \quad (4.2)$$

I(t) is given by

$$I(t) = \frac{1}{2\pi i}\int_{-i\infty+s}^{+i\infty+s} dp\, \frac{M}{k_{12}}(\alpha+p)(\beta+p)\bar{A}_2(p)e^{pt}. \quad (4.3)$$

The evaluation of Equation (4.3) leads to

$$I(t) = \frac{M}{k_{12}t_1}\left\{\left(\frac{1}{2} + \frac{t'}{2\sqrt{t'^2+d}}\right)\delta(t) + \frac{\alpha+\beta}{2}\left(1-\frac{t-t'}{\sqrt{(t-t')^2+d}}\right) + \ldots \right.$$

$$\left. \ldots + \alpha\beta\left(t_1 + \frac{1}{2}(t-t') - \frac{1}{2}\sqrt{(t-t')^2+d}\right) - \frac{1}{2}\frac{d}{\sqrt{(t-t')^2+d}^3}\right\} \quad (4.4)$$

Equation (4.4) shows that the shorter the rising time t_1 for amount $A_2(t)$, the larger must be the initial bolus. At the same time, the initial blood level rises like $1/t_1$, so that in actual dosage terms a compromise must be made between rapid saturation of the peripheral compartment and high initial blood levels. I(t) and the blood level c(t) is depicted in Figs. 4b and 4c. As a last example we wish to discuss the infusion scheme for sinus-like blood levels. Such a time course of blood levels (Fig. 5a) may be of interest in experimental clinical pharmacology, to estimate time constants and the reaction of involved structures (Segré 1968). Let

$$c(t) = \frac{A+B}{D}(M_1\sin(\omega t) + M_0) \quad \text{for } t \geqq 0$$

and

$$A_1(t) = M_1\sin(\omega t) + M_0, \quad M_0 \geqq M_1 \quad (5.1)$$

The Laplace transform $\bar{A}_1(p)$ of $A_1(t)$ is

$$\bar{A}_1(p) = \frac{M_0}{p} + \frac{M_1\omega}{p^2+\omega^2} \quad (5.2)$$

and hence

$$I(t) = \frac{1}{2\pi i}\int_{-i\infty+s}^{+i\infty+s} dp\, e^{pt}\bar{A}_1(p)G_1^{-1}(p). \quad (5.3)$$

Evaluation of the integral yields

$$I(t) = M_0\delta(t) + M_0k_{el} + \ldots$$

$$M_0k_{12}\left(1 - \frac{M_1\omega k_{21}}{M_0(k_{21}^2+\omega^2)}\right)e^{-k_{21}t} + \ldots$$

$$\ldots + M_1\varkappa(\delta_1\sin(\omega t) + \delta_2\omega\cos(\omega t)) \quad (5.4)$$

with

$$\varkappa = (A+B)/(A^2(\beta^2+\omega^2) + B^2(\alpha^2+\omega^2) + \ldots 2AB(\alpha\beta+\omega^2))$$

$$\delta_1 = A\alpha(\beta^2+\omega^2) + B\beta(\alpha^2+\omega^2)$$

$$\delta_2 = A(\beta^2+\omega^2) + B(\alpha^2+\omega^2).$$

The requirement $I(t) \geqq 0$ restricts the coefficients of (5.4) to the condition.

$$M_0k_{el} \geqq M_1\varkappa(\delta_1^2 + \omega^2\delta_2^2)^{1/2}.$$

This is essentially an upper limit for the frequency ω. It means it is impossible to achieve any arbitrary high or frequent change in blood level. Another remarkable point is the phase difference between $A_1(t)$ and I(t). The maximum of the infusion rate is achieved some time before the maximum of the blood level.

Microprocessor Controlled Infusion

In order to realize more elaborate infusion schemes, like those in the foregoing examples, it would be necessary to control the infusion pump automatically. We have interfaced a microprocessor (6502) to two pumps, so that the dosage of two drugs can be controlled simultaneously; in anaesthesia, for example, a hypnotic and an analgesic.

The microprocessor is programmed in such a way that three different kinds of administration, namely those of the first three examples given, are available, which can be combined in any way.

Input parameters are the pharmacokinetic data of the drugs to be infused, and parameters of the application scheme, such as the desired blood level, or amount in the peripheral compartment.

Since the maximum volume infusion rate is limited by the mechanics of the pump, a check is made whether the resulting infusion rate exceeds this limit. If this happens, the minimum drug concentration to be infused necessary to realize the scheme is given. Boluses to be given are also displayed. Since the infusion rate cannot be changed continuously, the real infusion scheme is a step function approximation of the ideal scheme. Due to mechanical inertia of the pump, the width of the steps cannot be chosen to be arbitrarily small. We used a step width of 15 s, which is large enough to calculate the next step and to avoid interference with the mechanics of the pump, and jet

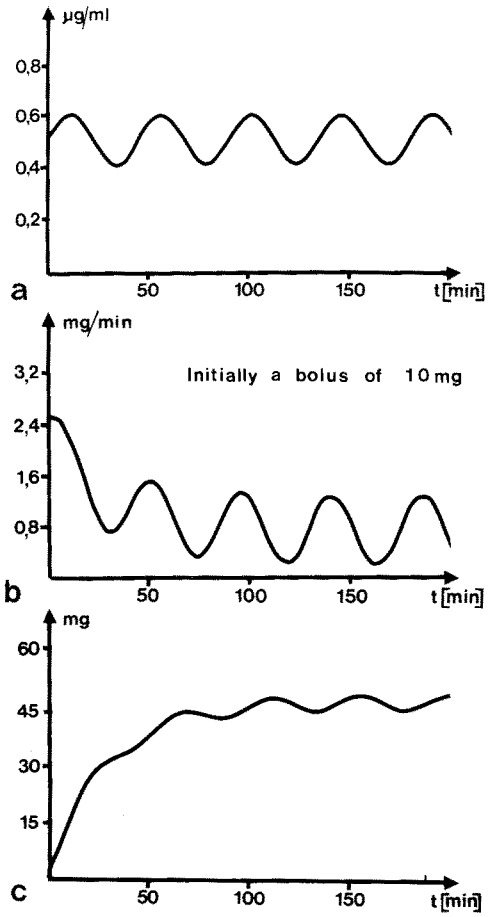

Fig. 5a–c. Sinus wave – like blood levels **a** require an infusion scheme like **b**. The resultant amount of drug in the peripheral compartment as depicted in **c**

is small enough with respect to circulation time. So far, the clinical utility of the device has been proven in 7 volunteers and 5 patients. For the group of volunteers we studied the models with constant blood level (first example) during Etomidate and Midazolam administration. In the patients we combined the first scheme for Etomidate with the second scheme for Fentanyl, to establish and maintain anaesthesia during surgery.

Discussion

The present approach gives a general method for calculation of an administration scheme from the desired blood levels and pharmacokinetic data. The clinical relevance of such elaborate dosage schemes may be questioned. As far as steady state conditions are concerned, the simple rule – the constant amount, which is eliminated per unit time must be administered as replacement – governs drug application. But the steady state has first achieved. For drugs with a large therapeutic index and for which steady state conditions are quickly reached, the simple steady state dosage rule may be sufficient for nearly optimal dosage.

For drugs with a small therapeutic index or for which the time interval over which they are administered, is in any way small in relation to their half life, it may be essential that the distribution phase is taken into account more exactly. This is commonly the case in anaesthesia. In our experience, microprocessor-controlled infusion is a convenient way to optimize application schemes in that area of drug treatment.

Appendix A

We are concerned with a general, linear n-compartment model. We assume that one can administer the drug in any compartment. Let $A_i(t)$ be the amount of drug in compartment i at time t, and $I_i(t)$ the amount of drug administered in compartment i per time at time t. The variation of $A_i(t)$ with time is described by

$$\frac{dA_i(t)}{dt} = \sum_{j=1}^{n} K_{ij}A_j(t) + I_i(t) \quad \text{for } i=1, \ldots, n. \tag{A.1}$$

(The K_{ij} are not the transfer constants but linear combinations of them.)

In matrix notation, abbreviating K_{ij} by $\mathbb{K}$ and A_i, and I_i by $\mathbf{A}$ and $\mathbf{I}$, (A.1) is shortened to

$$\frac{d\mathbf{A}(t)}{dt} = \mathbb{K}\,\mathbf{A}(t) + \mathbf{I}(t). \tag{A.2}$$

Assuming that the linear model is neither trivial nor degenerated, then $\mathbb{K}$ has n different eigenvalues $-\lambda_i$, $i=1, \ldots, n$ and a matrix $\mathbb{L}$ exists (Feldmann and Schneider 1976; Segré 1976) with

$$\mathbb{L}^{-1}\ \mathbb{K}\ \mathbb{L} = \begin{pmatrix} -\lambda_1 & \cdots & 0 \\ 0 & & -\lambda_n \end{pmatrix} \tag{A.3}$$

(A.2) can now be transformed to

$$\frac{d}{dt}\,\mathbb{L}^{-1}\mathbf{A}(t) = \mathbb{L}^{-1}\mathbb{K}\,\mathbb{L}\,\mathbb{L}^{-1}\mathbf{A}(t) + \mathbb{L}^{-1}\mathbf{I}(t). \tag{A.4}$$

Substituting (A.3) in (A.4) and solving the equation for the i-th component yields

$$(\mathbb{L}^{-1}\mathbf{A})_i(t) = e^{-\lambda i t} \int_0^t dt'\, e^{\lambda i t'} (\mathbb{L}^{-1}\mathbf{I})_i(t')dt'$$

multiplying by IL yields

$$A_i(t) = \int_0^t dt' \sum_{l=1}^{n} \left(\sum_{k=1}^{n} L_{ik}L^{-1}_{kl}\, e^{-\lambda_k(t-t')} \right) I_l(t'). \tag{A.5}$$

The function

$$G_{il}(t\text{-}t') = \begin{cases} 0 & \text{for } t<0 \\ \sum_{k=1}^{n} L^{-1}_{ik} L_{kl}\, e^{-\lambda_k (t-t')} & \text{for } t \geqq 0 \end{cases} \qquad (A.6)$$

is the Green's function of the system (A.1). It gives the amount of drug in compartment i at time t if a bolus of amount 1 was given at timt t′ in compartment l. $G_{il}(t-t')$ obeys the differential equation

$$\frac{d\, G_{il}(t-t')}{dt} = \sum_{k=1}^{n} K_{ik} G_{kl}(t-t') + \delta_{il}\delta(t-t').$$

δ_{il} denotes the unit matrix, namely say

$$\delta_{il} = \begin{cases} 0 \text{ for } i \neq l \\ 1 \text{ for } i = l \end{cases}$$

$\delta(t-t')$ denotes Dirac's delta function, which is the mathematical equivalent of a bolus of amount 1 at time $t=t'$.

With the abbreviation (A.6) Equation (A.5) may be written as

$$\mathbf{A}(t) = \int_0^t dt' G(t-t')\, \mathbf{I}(t'). \qquad (A.7)$$

Solving for $\mathbf{I}(t)$ in the same manner as in the examples yields

$$\mathbf{I}(t) = \frac{1}{2\pi i} \int_{-\infty+s}^{+i\infty+s} dp\, e^{pt}\, \bar{G}^{-1}(p)\, \bar{\mathbf{A}}(p). \qquad (A.8)$$

Knowing $\bar{G}^{-1}(p)$, (A.8) can be evaluated according to the rules of Appendix B.

$\bar{G}^{-1}(p)$ can easily be calculated:

$$G_{il}(t) = \sum_{k=1}^{n} L_{ik} L^{-1}_{kl}\, e^{\lambda_k t}$$

hence

$$\bar{G}_{il}(p) = \sum_{k=1}^{n} L_{ik} L^{-1}_{kl} \frac{1}{(p+\lambda_k)}$$

the inverse matrix is

$$\bar{G}^{-1}_{il}(p) = \sum_{k=1}^{n} L_{ik} L^{-1}_{kl} (p+\lambda_k) \qquad (A.9)$$

In developing the solution (A.8) it was assumed that the time course of the amounts of drug in all compartments are given, and that all compartments are accessible for dosing. If only k of the n possible amounts were prescribed, then only k compartments must be accessible for dosing.

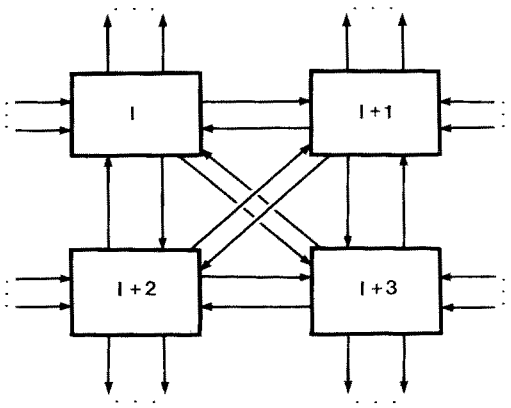

Fig. 6. Part of a general n-compartment model

The clinical by most important case is when the amount of drug in a compartment i is prescribed and the drug is administered in another, not necessarily different compartment j. In this case the equation

$$A_i(t) = \int_0^t dt' G_{il}(t-t')\, I(t')$$

with

$$G_{il}(t-t') = \sum_{k=1}^{n} L_{ik} L^{-1}_{kl}\, e^{-\lambda_k (t-t')}$$

has to be solved.

The solution, obtained by Laplace transformation, is

$$I(t) = \frac{1}{2\pi i} \int_{-i\infty+s}^{+i\infty+s} dp\, e^{pt}\, \Pi_{k=1}^{n} (p+\lambda_k) \Big/ \sum_{k=1}^{n} (L_{ik} L^{-1}_{kl} \prod_{j \neq k}^{n} (p+\lambda_j)) A_i(p). \qquad (A.10)$$

Up to the back transformation the dosage problem is reduced to the problem of finding out the eigenvalues of matrix $\mathbb{K}$ and the determination of matrix $\mathbb{L}$. Hence, the problem is reduced to discovering the eigenvalues and eigenvectors of $\mathbb{K}$ Standard programs for this problem exist for almost every scien tific computer language.

Appendix B

Integrals of the form

$$\frac{1}{2\pi i} \int_{-i\infty+s}^{+i\infty+s} dp\, e^{pt} f(p) \qquad (B.1)$$

must be interpreted as line integrals in the complex plane. The evaluation is most easily done in the framework of the theorem of residues.

The residues are determined by the poles and singularities of $e^{pt} f(p)$. These are the values of p for which $|e^{pt} f(p)|$ is greater than any real number.

The function $e^{pt}/(p+a)$ has, for instance, singularities at $p=+\infty$ and $p=-a$.

The following five rules allows integrals of the form (B.1) to be evaluated.

1. Determine which of both limits
$$\lim_{p\to\pm\infty} e^{pt}f(p)$$
is finite.
2. If the limit $p\to+\infty$ is finite, take into account all singularities at values of p with $Re(p)>0$. (Re(p) denotes the real part of p) If the limit $p\to-\infty$ is finite, take into account all singularities at values of p with $Re(p)\leqq 0$.
3. For special values of t the finite limit may be different from zero. This leads mathematically to a delta function, which corresponds to a bolus. The amount of the bolus is equal to the finite limit.
4. The function $e^{pt}\,f(p)$ may have poles of different order.
A pole of n-th order at $p=a$ is characterized by
$$\lim_{p\to a} |e^{pt}\,f(p)\,(p-a)^n| < \infty.$$
The residue of a pole of first order at $p=a$ is determined by
$$\lim_{p\to a} e^{pt}\,f(p)\,(p-a)$$
the residue of a pole of n–th order at $p=a$ is determined by
$$\lim_{p\to a} \frac{d^{n-1}}{dp^{n-1}} (e^{pt}\,f(p)\,(p-a)^n)$$
5. The value of the integral (B.1) equates sum of residues + sum of boli.
The residues of those poles whose p value is greater than or equal to zero must be multiplied by –1.

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