A METHOD FOR ACHIEVING RAPIDLY STEADY-STATE BLOOD CONCENTRATIONS OF I.V. DRUGS*

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SUMMARY

The theoretical basis of a pharmacokinetic method to obtain rapidly and maintain a steady plasma concentration of an i.v. drug is described. Computer simulations of morphine disposition in man, using pharmacokinetic constants obtained from the literature, are provided as examples of steady-state dose regimens. The usefulness and potential limitations of the method are discussed.

A basic assumption of the concept of "MAC"—the minimum alveolar concentration required to obtund the motor response of 50% of patients to a standard surgical incision—is that steady-state inhalation anaesthesia occurs with steady-state brain anaesthetic concentration. On the other hand, non-volatile anaesthetic drugs are usually given by intermittent i.v. injection, and as a result, there are wide fluctuations of blood and brain drug concentrations and the "level" of anaesthesia (Berkowitz et al., 1975; Murphy, Olson and Hug, 1979). This may explain why the use of narcotics, for example, may be associated with inadequate anaesthesia or analgesia and awareness during anaesthesia on the one hand, or unwanted effects such as nausea, vomiting, and postanaesthesia respiratory depression on the other hand (Rigg et al., 1978; Stapleton, Austin and Mather, 1979).

It seems logical, therefore, to use a more precise method of giving parenteral drugs to maintain a steady state of anaesthesia and analgesia.

This paper describes a theoretical analysis of a general method of infusing drugs to provide a steady-state concentration in the plasma. The method is a modification of the approach of Vaughan and Tucker (1976). These authors described a derivation of the ideal i.v. drug input required to achieve and maintain a constant plasma drug concentration. The results of computer simulation studies, using data from morphine obtained from the literature (Berkowitz et al., 1975), are described. Morphine was chosen for two reasons. First, it has been the subject of extensive pharmacokinetic analysis in animals and man, and its disposition is known to be consistent with an open two-compartment model with first-order drug elimination from the central compartment (Catlin, 1977). Second, morphine is widely used in medical, surgical and anaesthetic practice and the analysis is pertinent to all of these. In a companion paper, application of the method is described in experiments using fentanyl in the anaesthetized rabbit (Rigg et al., 1981).

The clinical objectives of general anaesthesia are rapid smooth induction, avoidance of toxicity and maintenance of a smooth plateau of surgical analgesia. The corresponding pharmacokinetic objectives of the method described here are to achieve steady-state plasma concentration \( C_{\text{r}} \) as quickly as possible and to place strict limits on deviations from the selected plasma concentration. In the present paper, a limit of \( \pm 20\% \) \( C_{\text{r}} \) achieved within 2 min of beginning morphine, was chosen.

THEORY

To clarify the rationale of combining a bolus injection with two or more consecutive constant infusions, pharmacokinetic theory is presented in four parts: (a) bolus injection, (b) constant-rate infusion, (c) combination of bolus injection with a
single constant-rate infusion and (d) combination of bolus injection with more than one constant-rate infusion.

(a) Bolus injection

If a single dose \( d \) of a drug is injected i.v., \( C_p \) at time \( t \), according to the two-compartment open model, will be given by the following equation:

\[
C_p = A e^{-\alpha t} + B e^{-\beta t} \quad \text{(fig. 1)}
\]

where

\[
A = \frac{Xd(\alpha - k_{21})}{V_1(\alpha - \beta)}
\]

\[
B = \frac{Xd(k_{21} - \beta)}{V_1(\alpha - \beta)}
\]

\[
V_1 = \frac{Xd}{A + B}
\]

(b) Constant-rate infusion

If a constant-rate infusion, \( Q \), is established, \( C_p \) at any time \( t \) after initiation of infusion is given by the equation (Greenblatt and Koch-Weser, 1975):

\[
C_p = \frac{Q}{V_1 k_{10}} \left[ 1 + \frac{(\beta - k_{10})}{\alpha - \beta} e^{-\alpha t} + \frac{(k_{10} - \alpha)}{\alpha - \beta} e^{-\beta t} \right] \quad \text{(2)}
\]

When it is sufficiently large, \( C_p \) will reach a steady-state \( C_p^{\infty} \), where \( C_p^{\infty} = \frac{Q}{V_1 k_{10}} \), which is independent of time. However, the establishing of a desired \( C_p^{\infty} \) using a single constant-rate infusion will take many hours. To overcome this problem, Wagner (1974) proposed a consecutive two rate-constant infusion method, to achieve \( C_p^{\infty} \) more rapidly. However, this method may necessitate an unacceptably long delay after beginning the infusion, before \( C_p^{\infty} \) is achieved.

(c) Combination of bolus injection and single constant-rate infusion

Equations (1) and (2) are graphically represented in figures 2 and 3, using the data of Berkowitz and others (1975), for morphine. These figures show an exponential decrease following i.v. bolus injection, and an exponential increase associated with constant-rate infusion, of drug concentration with time. Intuitively, it seems that combining these two approaches may achieve \( C_p^{\infty} \) around \( C_p^{\infty} \). The single loading dose \( Xd \) required to achieve \( C_p^{\infty} \) almost instantaneously, is:

\[
Xd = C_p^{\infty} \cdot V_1 \quad \text{(3)}
\]

The constant infusion rate, \( Q^{\infty} \), that will achieve \( C_p^{\infty} \) eventually is:

\[
Q^{\infty} = C_p^{\infty} \cdot V_1 \cdot k_{10} \quad \text{(4)}
\]

If this loading dose is combined with this constant infusion (Boyes et al., 1971), \( C_p \) at any time \( t \) is given by:

\[
C_p = \frac{Q^{\infty}}{V_1 k_{10}} + F e^{-\alpha t} + G e^{-\beta t} \quad \text{(5)}
\]

where

\[
F = \frac{(\alpha Xd - Q^{\infty})(k_{10} - \beta)}{V_1 k_{10}(\alpha - \beta)} \quad \text{(6)}
\]

and

\[
G = \frac{(\beta Xd - Q^{\infty})(\alpha - k_{10})}{V_1 \cdot k_{10}(\alpha - \beta)} \quad \text{(7)}
\]

From equation (5) it can be seen that \( C_p \) is not constant as \( t \) changes. However, when \( t \) is very
STEADY-STATE BLOOD DRUG CONCENTRATIONS

Fig. 2. Computer-predicted plasma concentration–time relationship for morphine after bolus dose, $X_d$ at time $t = 0$. Prediction based on data of Berkowitz and others (1975).

Fig. 3. Computer-predicted plasma concentration–time relationship for morphine after constant-rate infusion beginning at time $t = 0$. Prediction based on data of Berkowitz and others (1975).
large, $e^{-\alpha t}$ and $e^{-\beta t}$ approach 0 and $C_p$ will approximate $Q^*V_1/k_{10}$ (that is, $C_p^*$).

A typical curve for morphine, from the data of Berkowitz and others (1975) described by equation (5), is shown in figure 4. In this example, $C_p$ decreases to 35% of $C_p^*$ at $t = 7.5$ min, at which moment it begins to increase again, reaching 80% of $C_p^*$ at 100 min. Clearly, such a curve exceeds the predetermined limit of ±20% $C_p^*$.

Intuitively, it seems possible that this problem might be overcome by the procedure of Mitenko and Ogilvie (1972) who proposed a larger loading dose:

$$X_d = C_p^*V^\beta$$

(8)

where

$$V^\beta = V_1/k_{10}/\beta$$

Mitenko and Ogilvie (1972) combined this loading dose with the constant-rate infusion, $Q^*$, a procedure that they showed to be relatively safe for theophylline. When this large loading dose is substituted in equation (5), the term $G$ equals 0, and $C_p$ will never decrease to less than $C_p^*$ (fig. 5). However, morphine and most other lipid-soluble anaesthetic drugs are distributed extensively into a peripheral compartment. This causes a relatively high ratio of initial to steady-state plasma concentration ($C_p^0:C_p^*$; for Berkowitz and others' (1975) morphine data = 6.3:1). Consequently, an unacceptably high initial $C_p$ may occur, as is evident in figure 5.

The effect of a loading dose for morphine, intermediate between the two values described by equations (3) and (8), is shown in figure 6, which shows predicted concentration–time profiles when $Q^*$ is combined with three different bolus doses: (1) $X_d = 1/2 C_p^*(V^\beta + V_1)$; (2) $X_d = 1/3 C_p^*V^\beta$ and (3) $X_d = 1/6 C_p^*V^\beta$. None of these curves is satisfactory. Either $C_p$ is too great initially, or too small before $C_p^*$ is obtained.

(d) Combination of loading dose with more than one consecutive constant-rate infusion

The computer simulated curves of figure 6 substantiate the prediction of Kruger-Thiemer (1968) that, for a system with more than one compartment, a desired blood concentration cannot be achieved rapidly and maintained by any choice of a single i.v. loading dose and a single constant infusion rate. More recently, Vaughan and Tucker (1976) described a general method for ideal drug input to achieve rapidly and maintain a desired $C_p^*$. Their method incorporates a loading...
Fig. 5. Computer-predicted plasma concentration–time relationship for morphine using the procedure of Mitenko and Ogilvie (1972), for combined bolus and constant-rate infusion doses. Prediction based on data of Berkowitz and others (1975).

Fig. 6. Computer-predicted plasma concentration–time relationship when a constant-rate infusion is begun with three different bolus doses, intermediate in magnitude to those calculated by the methods of Boyes and others (1971) (fig. 4) and Mitenko and Ogilvie (1972) (fig. 5). Predictions based on data of Berkowitz and others (1975). See text for further details.
dose $X_d$ (equation (3)), a constant rate infusion (equation (4)) and an infusion rate exponentially decreasing with time according to the following expression:

$$Q_e = X_d U_1 \cdot k_{21} \cdot e^{-k_{21}t} \quad (9)$$

where

$$U_1 = (\alpha - k_{21}) (\beta - k_{21})^2.$$  

The plasma concentration, $C_{pe}$ resulting from the exponential infusion $Q_e$ is given by the convolution integral:

$$C_{pe} = Q_e(t) * \sum_{i=1}^{2} A_i \cdot e^{-\alpha_i t} \quad (10)$$

$$= \int_0^t Q_e(\tau) A_i e^{-\alpha_i (t-\tau)} d\tau \quad (11)$$

where

$$\sum_{i=1}^{2} A_i e^{-\alpha_i t}$$

is the response of the two compartment system to a unit impulse input and

$$A_1 = \frac{(\alpha - k_{21})}{V_1(\alpha - \beta)}$$

and

$$A_2 = \frac{k_{21} - \beta}{V_1(\alpha - \beta)} \cdot A_1, \quad A_2, \quad \alpha_1 \quad \text{and} \quad \alpha_2$$

are notations used by Vaughan and Tucker and are related to parameters used in this paper, as follows:

$$A_1 = \frac{A}{X_d}, \quad A_2 = \frac{B}{X_d}, \quad \alpha_1 = \alpha \quad \text{and} \quad \alpha_2 = \beta$$

With $Q_e(t)$ substituted by equation (9), and after integration and simplification, equation (11) becomes:

$$C_{pe} = \frac{X_d (\alpha - k_{21}) (k_{21} - \beta)}{V_1 \cdot k_{21} (\alpha - \beta)} \cdot (e^{-\beta t} - e^{-\alpha t}) \quad (12)$$

Since $C_{pe} = Q_{pe}/V_1 \cdot k_{10}$, $Q_{pe} = X_d k_{10}$, and $k_{10} = \alpha \beta / k_{21}$, equation (5) can be simplified to:

$$C_p = C_{pe} + \frac{X_d (\alpha - k_{21}) (k_{21} - \beta)}{V_1 k_{21} (\alpha - \beta)} \cdot (e^{-\alpha t} - e^{-\beta t}) \quad (13)$$

The sum of equations (12) and (13) is $C_{pe}$. Hence, the plasma concentration attributable to the loading dose $X_d$ (equation (3)), the constant-rate infusion $Q^*_{m} \quad (equation (4))$ and an exponential infusion (equation (9)), combined, is $C_{pe}$ at all times. In other words, a steady plasma concentration can be obtained almost instantaneously and maintained indefinitely by a combination of these three doses. An exponentially decreasing infusion rate could be provided by a specially designed pump. However, this approach is not favoured by us because of the increased difficulties for the clinician in conceiving quantitatively both dose and rate of dosing with a system incorporating an infusion rate that is continually changing. To overcome this problem, the exponentially decreasing infusion rate may be approximated by a series of fixed duration sequential constant rate infusions.

Since the rate of exponential infusion at time $t = X_d U_1 \cdot k_{21} \cdot e^{-k_{21}t}$, the cumulative infusion from time $t = 0$ to time $t$ is:

$$\int_0^t X_d U_1 \cdot k_{21} \cdot e^{-k_{21}t} dt = X_d U_1 (1 - e^{-k_{21}t}) \quad (14)$$

The cumulative infusion time curve has the general features given by the plot of $1 - e^{-k_{21}t}$ vs. time (fig. 7). This curve can be approximated by any number of sequential linear segments; the greater the number, the more closely the series of linear functions approximates the exponential function. In figure 7, four segments are chosen to approximate the curve of four consecutive time periods. Each successive infusion rate is a function of the slope of corresponding successive segments of the exponential curve. For example,

$$Q_1 e = \text{Slope} \cdot S_1 \cdot (-X_d U_1), \quad \text{infusion rate, given from time} \quad t = 0 \quad \text{to} \quad t_1$$

$$Q_2 e = \text{Slope} \cdot S_2 \cdot (-X_d U_1), \quad \text{infusion rate, given from time} \quad t_1 \quad \text{to} \quad t_2$$

$$Q_3 e = \text{Slope} \cdot S_3 \cdot (-X_d U_1), \quad \text{infusion rate, given from time} \quad t_2 \quad \text{to} \quad t_3$$

$$Q_4 e = \text{Slope} \cdot S_4 \cdot (-X_d U_1), \quad \text{infusion rate, given from time} \quad t_3 \quad \text{to} \quad t_4$$

### APPLICATION

The method was tested by computer simulation. A computer program (VANDT, Fortran IV, CDC 6400) was written to permit calculation of a dosage schedule based upon known pharmacokinetic parameters. The desired $C_{pe}$ and the maximum allowable fluctuation from $C_{pe}$,
STEADY-STATE BLOOD DRUG CONCENTRATIONS

TABLE I. Pharmacokinetic parameters of individual subjects and pooled data of subjects of Berkowitz and others (1975)

<table>
<thead>
<tr>
<th>Subject</th>
<th>A (g ml⁻¹)</th>
<th>α (h⁻¹)</th>
<th>B (g ml⁻¹)</th>
<th>β (h⁻¹)</th>
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<tr>
<td>1</td>
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<td>0.1109</td>
<td>-0.5377</td>
</tr>
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<td>0.08741</td>
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</tr>
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<td>-0.8747</td>
</tr>
<tr>
<td>5</td>
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<td>0.13712</td>
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<tr>
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<tr>
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<td>0.10410</td>
<td>-0.9486</td>
</tr>
<tr>
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<td>0.1214</td>
<td>-0.8033</td>
</tr>
</tbody>
</table>

From equation (4):

\[ Q^* = C_p^* \cdot V_1 \cdot k_{10} = 0.0055 \text{ mg kg}^{-1} \text{ min}^{-1} \]

Since \( Q_1, Q_2, \text{ and } Q^* \) are constant rate infusions, \( Q_1, Q_2 \), and \( Q^* \) are added to give a new constant rate infusion \( Q_1 \), and \( Q^* \) becomes \( Q_2 \).

The final dose schedule is:

1. \( Xd \ 6.5 \text{ mg kg}^{-1} \) given at \( t = 0 \)
2. \( Q_1 \ 0.019 \text{ mg kg}^{-1} \) given from 0 to 15
3. \( Q_2 \ 0.0055 \text{ mg kg}^{-1} \) given from 15 min indefinitely.

Computations for \( C_p^* = 400, 300, 200 \) and 100 ng ml⁻¹ are plotted in figure 8. For each, the least deviation of \( C_p^* \) was 82%, occurring at 3 min and the greatest deviation was 115% of \( C_p^* \) at 15 min.

If more than two different consecutive constant-rate infusions are used, then the predetermined steady-state drug concentration can be simulated more precisely and a more narrow limit of fluctuation defined. Greater precision (lower predicted drug concentration fluctuations) can be achieved at the expense of simplicity (a larger number of consecutive infusions will be required). The computer program requires the pharmacokinetic model parameters and the pre-selected drug concentration and fluctuation limits. Given this information, the program prints out the least number of infusions required to maintain \( C_p^* \) within this limit.
FIG. 8. Computer-predicted plasma concentration–time relationships for morphine to achieve $C_{pss} = 400$, 300, 200, and 100 ng ml$^{-1} \pm 20\%$. Predictions based on data of Berkowitz and others (1975). See text for further details.

FIG. 9. Computer-predicted plasma concentration–time relationships for individual subjects of Berkowitz and others (1975). The infusion regimen was determined from the pooled data of Berkowitz and others (1975). Deviation from predicted is a measure of the extent of the error which can be expected from using pooled data to predict individual steady-state plasma morphine concentrations.
The original parameters for the pooled and individual data of Berkowitz and others (1975) are given in table I. An estimate of the probable range of responses in individual subjects is given by computer simulations of predicted steady-state plasma morphine concentrations in some of Berkowitz and others' subjects given the above regimen. These simulations are shown in figure 9. They were chosen from the most "outlying" of Berkowitz and colleagues' subjects (table I). Thus, the estimates of $C_p$ shown in figure 9 represent the probable worst cases of deviation from target $C_p^{"w}$ as a result of the error inherent in using pooled data to predict individual responses. In all cases an approximate steady state is present by 30 min, and initial plasma concentrations range from transient high of almost four times $C_p^{"w}$ to an initial low concentration of 30%.

**DISCUSSION**

This paper describes a general method, modified from Vaughan and Tucker (1976), for obtaining rapidly and maintaining steady-state plasma concentrations of drugs given i.v. The mean data of Berkowitz and others (1975) for the disposition of morphine are used to calculate a regimen for i.v. morphine to maintain plasma concentration within 20% of the desired concentration after an initial bolus injection.

Although the mathematical analysis appears complicated, the practical application of the method is relatively straightforward using a computer. The computer-simulated curves described in this paper suggest that the method could improve precision of control of plasma drug concentration.

Some practical limitations of the method are suggested. First, if there is wide inter-individual variation in $V_1$, or $k_{10}$, an infusion regimen developed from averaged data will have limited precision when applied to individual patients. The extent of this limitation depends on the degree of inter-individual variation. Further experiments are required for different drugs to compare the precision of the method for individual and group predictions. It is likely that, for most drugs, there will be greater inter-individual variation of $k_{10}$ than of $V_1$, a consequence of the many physiological factors contributing to inter-individual variation in drug disposition. Second, another potential source of error may occur in the estimation of $A+B$, required to estimate $V_1$; individual studies of different drugs are needed, with rigorous attention to the timing of frequent blood samples, during the distribution phase, to quantitate this error and the physiological factors that influence it.

A further possible limiting factor in the application of the method is the extent to which the behaviour of a drug in the body deviates from the assumptions of the pharmacokinetic model. The model assumes that mixing of the drug in the central compartment is instantaneous and complete. For most drugs the central compartment volume represents approximately the circulation volume and a component of the extracellular fluid volume of organs with a very high blood flow (heart, brain, kidney and liver). Mixing is probably very rapid in this compartment, but it is not instantaneous. Thus, during the 2–3 min following an i.v. bolus, a plasma sample from either venous or arterial blood may not precisely reflect "mean" central compartment concentration ($C_1$). If mixing is incomplete, plasma samples will, in most cases, underestimate $C_1$. This difficulty is compounded by another problem: the rapidly injected bolus might cause an acute toxic effect on the myocardium as a result of the sudden exposure of the heart to a brief period of extremely high drug concentration as the venous "slug" is returned to the right side of the heart (Goldstein, Aronow and Kalman, 1968). These problems may introduce further errors in estimating $V_1$. They may be minimized by giving the bolus as a brief infusion to allow for near complete mixing before sampling blood for drug analysis. The determination of the pharmacokinetic disposition parameters when the initial bolus is administered as a brief infusion, requires the correction described by Loo and Riegelman (1970).

The data of Berkowitz and others (1975) were obtained from surgery patients known not to have intercurrent medical disorders. However, many different medical disorders can affect drug disposition and elimination; the extent to which such disorders prevent effective application of this approach remains to be determined.

The general utility of the technique depends on how closely biological effect is correlated with blood concentration of drug in a steady state. This is largely unknown for most i.v. drugs and also requires experimental testing. Given the assumption that biological effect does closely parallel blood and tissue concentration in the
steady state, the technique has the advantage of providing rapid onset and smooth maintenance of effect and minimum toxicity. This would seem to be a desirable objective for the use of all drugs given i.v.

Pharmacokinetic analyses of the uptake and distribution characteristics of inhaled anaesthetics, and clinical experience, suggest that steady-state plasma concentration of these drugs provides steady anaesthesia effect. *A priori*, it is reasonable to expect that this also would hold true for drugs given parenterally. That such simple relationships need not exist in the unsteady or transient state was shown by Finck and others (1977), who studied morphine disposition in blood and brain following i.v. injection in the dog. These authors showed that $T_1$ of brain morphine was 4.1 h in contrast to $T_j$ for serum morphine of 1 h. They interpreted their results by suggesting that, once morphine enters the brain, the greater proportion of the drug was converted to the protonated form, thus providing less free base available to cross the blood–brain barrier and return to the circulation. This observation suggests that, after a bolus, a concentration gradient may exist between brain and plasma and that biological effect may be greater than expected and more prolonged than plasma concentrations would suggest. However, if steady-state morphine concentration is achieved in plasma, it is reasonable to predict that a steady morphine concentration will be achieved in the brain also within 20–30 min, and that this would be associated with a steady central pharmacological effect. Finck and others (1977) also showed the importance of $P_{CO_2}$ as a determinant of serum and brain morphine disposition. During hypercapnia, they showed a 40% decrease in $V_1$ and a corresponding increase in plasma morphine concentration. It is not known whether this is a general effect of $P_{CO_2}$ on drug distribution, an effect mediated via the influence of carbon dioxide on the cerebral circulation and cardiac output, a specific effect on the morphine molecule, or a combination of these. In a subsequent study these investigators showed that hypocapria also led to increased plasma morphine concentrations; clearly, different mechanisms were operative in this situation (Nishateno et al., 1979). Both studies indicate that, in studies of constant plasma concentration kinetics, it is important to control acid–base variables.

The potential of this theoretical approach to obtain steady-state drug concentration and effect justifies further study in healthy subjects and with computer simulation techniques, using drugs such as the muscle relaxants, narcotics and barbiturates in which both drug concentration and drug effect can be measured precisely.

**APPENDIX**

**GLOSSARY OF ABBREVIATIONS**

$V_1 =$ apparent volume of the central compartment

$V_2 =$ apparent volume of the peripheral compartment

$V^d =$ apparent volume of distribution of drug in post-distributive phase

$C_1 =$ concentration of drug in the central compartment

$C_2 =$ concentration of drug in the central compartment

$C_p =$ concentration of drug in the plasma

$C_{pe} =$ concentration in the plasma at steady state

$C_{br} =$ mean concentration of drug in brain tissue

$C_{c} =$ mean concentration of drug in the central compartment at $t = 0$

$C_{ce} =$ mean concentration of drug in the central compartment at equilibrium

$t =$ time after i.v. injection

$k_{12} =$ first order rate constant for drug transfer from the first to the second compartment

$k_{21} =$ first order rate constant for drug transfer from the second to the first compartment

$k_{1s} =$ first order rate constant for drug elimination from the central compartment

$A, B =$ hybrid constants, each a complex function of the parameters of the model

$X_d =$ i.v. loading dose, given at time $t = 0$

$e =$ exponential constant

$Qe =$ exponentially decreasing infusion rate of Vaughan and Tucker’s (1976) method

$Q_{1e} =$ a component of the drug infusion rate from 0 to 15 min

$Q^e =$ steady state drug infusion rate from 15 min to infinity

$Q_i =$ drug infusion rate from 0 to 15 min ($Q_{1e} + Q^e$)

$F, G =$ symbols used for complex functions of model parameters in the equation derived as a general expression for $C_p$ when a loading dose is combined with a constant-rate infusion

$U_1 =$ a constant derived from model parameters, and used by Vaughan and Tucker to compute an exponential infusion rate

$t_1 =$ Time duration of first constant rate infusion, in relation to time of administration of bolus dose

$T_i =$ half-life (time for halving of drug concentration)

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NOTE: The program listing for the program to compute infusion regimens from pharmacokinetic constants (VANDT) is available from the corresponding author.

REFERENCES

METHODE PERMETTANT D'ATTEINDRE RAPIDEMENT UN EQUILIBRE CINETIQUE DES CONCENTRATIONS DE MEDICAMENTS ADMINISTRES PAR VOIE INTRAVEINEUSE

RESUME
Nous decrivons dans cet article la base theorie de une methode pharmacocinetique permettant d'obtenir rapidement et de maintenir dans le plasma une concentration constante du medicament administre par voie intraveineuse. Nous donnons comme exemples des doses de regimes d'equilibre cinetique des simulations par ordinateur de la disposition de la morphine chez l'homme, en nous basant sur des constantes pharmacocinetiques obtenues dans les livres. L'utilite et les limites eventuelles de cette methode sont largement debattues.

EINE METHODE ZUR SCHNellen HERSTELLUNG VON STATIONAren BLUTKONZENTRATIONEN VON INTRAVENOS VERABREICHTEN DROGEN

ZUSAMMENFASSUNG

METODO PARA LOGRAR RAPIDAMENTE CONCENTRACIONES DE ESTADO DE REGIMEN DE DROGAS ADMINISTRADAS INTRAVENOSAMENTE

SUMARIO
Se describe la base teórica de un método farmacocinético para obtener rápidamente y para mantener una concentración constante en el plasma de una droga administrada intravenosamente. Se proveen simulaciones mediante ordenador de la disposición de la morfina en el hombre, haciendo uso de constantes farmacocinéticas obtenidas de la literatura existente, a guisa de ejemplos de las condiciones de dosis en el estado de régimen. Se discuten la utilidad y las limitaciones potenciales del método.