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# A Technique for Approximately Maintaining Constant Plasma Levels of Intravenous Drugs

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***Background:*** **There is increasing interest among anesthesiologists in the use of continuous infusion of intravenous drugs. The therapeutic effect of most drugs is a function of the concentration at the site of drug effect, which in turn is determined by the plasma concentration. Constant plasma concentrations can be maintained by computer-controlled infusion pumps. However, such equipment is not yet widely available and will be expensive.**

***Methods:*** **A technique is presented to enable the anesthesiologist to maintain approximately a desired plasma concentration after an arbitrary bolus dose by using a series of infusions with rates decreasing in a stepwise fashion. The algorithm is based on approximating the exact infusion needed to maintain the target plasma concentration by producing this concentration at discrete, specific times. Equations are derived for calculating the sequential rates of the infusion scheme. The equations assume linear pharmacokinetics, and the starting point for derivation of the equations is the assumption that the plasma concentration is given by the convolution of the drug infusion and the unit dose-response function.**

***Results:*** **The accuracy of the technique was assessed by simulating the infusion of fentanyl and midazolam. By using an infusion scheme of three steps, the error was no greater than 38% for fentanyl and no greater than 10% for midazolam.**

***Conclusions:*** **Other than the assumption of linear kinetics, the algorithm is independent of pharmacokinetic models. Implementation does not require computer-based numerical analysis. (Key words: Anesthetic techniques: continuous infusion. Pharmacokinetics: linear systems.)**

WITH many intravenous drugs, the most rational and efficient method of administration is by a continuous infusion. While intravenous anesthetic agents ultimately must be titrated to effect, nevertheless their use is facilitated by a knowledge of therapeutic plasma levels and by administration in a manner designed to achieve these levels. To achieve and maintain a constant plasma level, the drug must be given as an initial bolus (loading) dose in conjunction with an infusion at a rate equal to a constant term plus one or more exponentially decreasing terms.[1] This type of infusion scheme is possible using computer-controlled pumps.[2] However, these systems are not yet widely available. Furthermore, in an age of increasing concern about health care costs, the expense of the computer/pump system may prove prohibitive in many settings. In the absence of this technology, the anesthesiologist can approximate the continuously varying infusion by a series (two or more) of constant-rate infusions, the rates of which decrease in a stepwise manner. This paper describes a technique for calculating the rates of the sequential infusions necessary to approximate a constant plasma level. The technique is analytic, does not require a computer for implementation, and is independent of specific pharmacokinetic models.

## Methods

The target plasma concentration of an intravenous drug ($C_0$) can be achieved asymptotically as the duration of the infusion approaches infinity by a continuous infusion at a rate calculated as the product of $C_0$ and the drug clearance.[3] Furthermore, the clearance can be defined as the inverse of the area under the curve (AUC) that describes the concentration in plasma after a single dose of unit magnitude as a function of time. For reasons that will become evident, this parameter will be denoted as $AUC(\infty)$. In Appendix 1, it is demonstrated that to achieve the desired target concentration $C_0$ at some specific time t using a single constant-rate infusion, the magnitude of this infusion must be equal to $C_0/AUC(t)$, where AUC(t) is the area under the concentration *versus* time curve after a single unit magnitude dose from time zero to time t (fig. 1). (It is important to note that AUC(t) is normalized as the area under the curve *divided* by the dose.) Using this basic observation, equation A10 is derived and used to determine the infusion rates $I_1$, $I_2$, and $I_3$ needed to produce the desired plasma concentration $C_0$ at the times $t_1$, $t_2$, and $t_3$ after an arbitrary initial bolus dose. The

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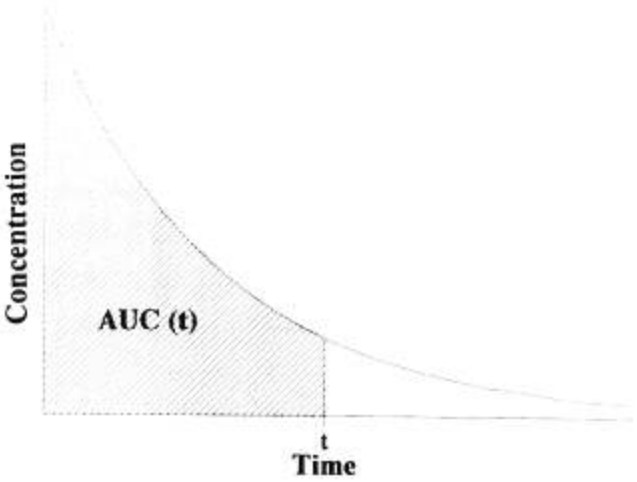


**Fig. 1. AUC( $\infty$ ) is defined as the area under the curve expressing concentration as a function of time after a single dose. AUC(t) is the area under the curve to time t.**

hypothesis of this paper is that the desired plasma concentration $C_0$ can be approximately maintained as long as necessary by achieving it at specific points (*i.e.*, $t_1$, $t_2$, $t_3$). As the number of specific points at which the concentration is exactly $C_0$ increases, the error of the approximation decreases.

As written, equation A10 is imposing and does not readily lend itself to clinical application. However, this equation can be simplified for the conditions that are likely to be encountered in clinical practice. First, it is likely that few anesthesiologists will find it convenient to change infusion rates more than two times, *i.e.*, the number of steps in the infusion sequence will be three or less. Second, the terminal infusion will be equated with the infusion rate needed to maintain the target plasma concentration after the steady state is achieved. This is done to avoid exceeding the target plasma concentration if the duration of the infusion becomes excessive.

With these assumptions the algorithm to approximately maintain a constant $C_0$ is as follows. An initial bolus dose is given. This dose is essentially arbitrary but could be the dose needed to rapidly produce the desired plasma concentration or, in the case of drugs more slowly equilibrating with the central nervous system, the dose needed to rapidly produce the desired "effect site" concentration. The issue of calculating the initial bolus dose is discussed elsewhere.[4] The algorithm of this paper is designed to accommodate the bolus dose believed to be clinically indicated. To proceed, the anesthesiologist will have selected two times, denoted $t_1$ and $t_2$, when it is believed the target concentration $C_0$ should be *exactly* achieved. Since, as will be seen, the algorithm errs by underachieving the target concentration, it will be appropriate that these be points of significant surgical stimulation. For example, at our institution, surgical incision usually occurs approximately 30 min after induction so that, in the simulations used in this paper, $t_1$ will be equal to 30. Also, $t_2$ will be set equal to 120 min, corresponding to a surgical procedure in which intense stimulation persists for approximately 90 min after incision, followed by the less intense period of surgical closure.

Following the initial bolus an infusion, $I_1$, is begun. The rate of this infusion, derived from equation A10, is given by

$$I_1 = \frac{C_0 - C_b(t_1)}{AUC(t_1)} . \quad (1)$$

$C_b(t_1)$ is the concentration resulting from the bolus dose at time $t_1$ and $AUC(t_1)$ is the parameter illustrated in figure 1. Calculation of these variables is discussed below.

The infusion $I_1$ is continued to the time $t_1$ at which point the rate is lowered to $I_2$, given by (and again derived from equation A10)

$$I_2 = \frac{C_0 - C_b(t_2) - I_1[AUC(t_2) - AUC(t_2 - t_1)]}{AUC(t_2 - t_1)} . \quad (2)$$

To clarify, notation $AUC(t_2-t_1)$ is the function illustrated in figure 1 with the argument t made equal to $t_2-t_1$.

Finally, at time $t_2$ the infusion rate is lowered to the steady-state value $I_3$.

$$I_3 = \frac{C_0}{AUC(\infty)} \quad (3)$$

In some cases it might be appropriate to utilize a two-step rather than three-step infusion scheme. In this case the initial bolus is followed by infusion $I_1$ designed to exactly achieve the desired plasma concentration after an interval $t_1$. The rate of this infusion is given by equation 1. At time $t_1$, the rate of the infusion is simply reduced to the steady-state value given by equation 3.

To utilize these equations, the terms AUC(t) and $C_b(t)$ must be defined. The kinetics of almost all drugs employed in anesthesiology can be described by bi- or tri-exponential equations. Specifically, $C_b(t)$, the plasma concentration that results from a bolus dose in B units ($\mu$g, mg, or other, as appropriate) is given by

$$C_b(t) = B[A_1 \exp(-k_1 t) + A_2 \exp(-k_2 t) + A_3 \exp(-k_3 t)]. \quad (4)$$

Note that for drugs with bi-exponential kinetics, the coefficient $A_1$ is set equal to zero.

This equation defines the term $C_b(t)$ in equations 1 and 2. The other parameter, AUC(t), needed to calculate the infusion rates is derived by integrating the above equation and is given by

$$(A_1/k_1)[1 - \exp(-k_1 t)] + (A_2/k_2)[1 - \exp(-k_2 t)] + (A_3/k_3)[1 - \exp(-k_3 t_1]. \quad (5)$$

For example, if $t_2 = 120$ and $t_1 = 30$, then $AUC(t_2 - t_1)$ is equal to

$$(A_1/k_1)[1 - \exp(-90k_1)] + (A_2/k_2)[1 - \exp(-90k_2)] + (A_3/k_3)[1 - \exp(-90k_3)].$$

Also note that

$$AUC(\infty) = (A_1/k_1) + (A_2/k_2) + (A_3/k_3). \quad (6)$$

Implementation of equations 1–6 was exemplified and the accuracy of the algorithm was assessed by simulating the infusion of fentanyl (after bolus doses of 25 or 150 μg) with a plasma target concentration of 2 ng/ml and by simulating the infusion of midazolam (after a bolus dose of 44 μg/kg) with a plasma target concentration of 100 ng/ml. The infusion of midazolam using a two-step rather than three-step scheme also was simulated and compared to the plasma concentrations that result from a bolus dose followed by the steady-state infusion of equation 3.

Pharmacokinetic data were taken from reference 5. Specifically, table 1 of this reference lists the parameters of the unit disposition function, *i.e.*, the function describing the plasma concentration resulting from a unit (1 μg, 1 mg, or other as appropriate) bolus dose for fentanyl and midazolam. Plasma concentrations resulting from the various infusion schemes were calculated from equation A1.

## Results

Hughes, Glass, and Jacobs report a volume of the central compartment for fentanyl of 13 L.[5] Note that their pharmacokinetic parameters for fentanyl are not normalized to body weight. Thus to achieve a plasma concentration of 2 ng/ml, a bolus dose of 26 μg would be required. The actual plasma concentration that would result from a bolus dose of this magnitude with the infusions calculated in the previous section is shown in figure 2. It will be noted that the effect of this infusion scheme is to achieve exactly the desired plasma concentration at the time of the initial bolus and at 30 min and 120 min. Between these times and after $t_2$, the plasma concentration is less than the target value. The maximum error, expressed as a percentage of the target plasma concentration, is 38%. The maximum error occurs shortly (5 min) after the beginning of the infusion, and the error quickly diminishes. In the simulated case, this would be between intubation and incision. Figure 2 also reveals that the plasma concentration steadily decreases during the terminal phase of the infusion because of use of the steady-state infusion rate (equation 3).

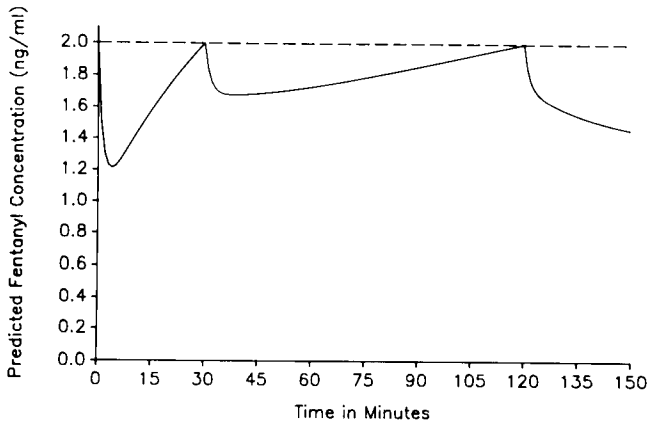


**Fig. 2. Plasma fentanyl concentration after a bolus dose of 25 μg and infusions $I_1$ (0–30 min), $I_2$ (30–120 min), and $I_3$ (120–150) of 7.4, 4.2, and 1.5 μg/min, respectively. The kinetic data used for this simulation were not normalized to body weight.[5] The dashed line indicates the target concentration of 2 ng/ml.**

Bolus doses of fentanyl used in clinical practice are much larger than that calculated above on the basis of the volume of the central compartment, because this calculation does not account for the significant distribution out of the central compartment that occurs while the drug reaches the site of its effect in the central nervous system.[3] Infusion rates necessary to achieve a plasma concentration of 2 ng/ml after a more clinically realistic bolus dose of 2 μg/kg were calculated as noted in the previous section. The actual plasma concentration that would result from this bolus dose with the infusion rates noted are shown in figure 3. The initial concentrations will be higher than the target and would likely speed the rise of fentanyl concentration in the central nervous system and allow for the effective blunting of responses to laryngoscopy and tracheal intubation. The exact target plasma concentration again

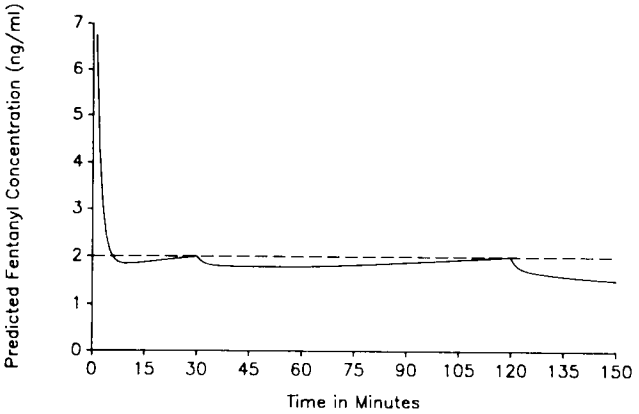


**Fig. 3. Plasma fentanyl concentration after a bolus dose of 150 μg and infusions $I_1$ (0–30 min), $I_2$ (30–120 min), and $I_3$ (120–150 min) of 5.7, 3.9, and 1.5 μg/min, respectively. The kinetic data set used for this simulation was not normalized to body weight.[5] The dashed line indicates the target concentration of 2 ng/ml.**

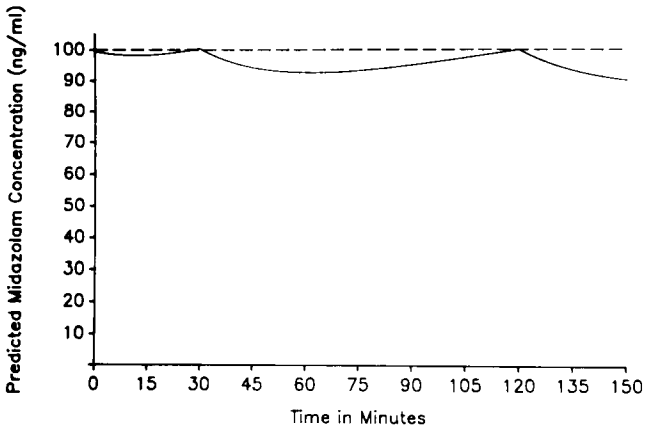


**Fig. 4. Plasma midazolam concentration after a bolus dose of 44 μg/kg and infusions $I_1$ (0–30 min), $I_2$ (30–120 min), and $I_3$ (120–150 min) of 1.5, 1.1, and 0.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively. The dashed line indicates the target concentration of 100 ng/ml.**

is achieved at 30 and 120 min, and between these points the actual plasma concentration is less than the target.

A simulated infusion of midazolam is presented in figure 4 with a target plasma concentration of 100 ng/ml. Two sequential infusions were employed with $t_1$ of 30 min and $t_2$ of 120 min. The maximum error is 10%. The maximum error again occurred during the terminal phase of the infusion, when the steady-state infusion rate is used.

A more simplified infusion of midazolam using a bolus dose and a two-step infusion is presented in figure 5. This is compared to the plasma concentration that results from the common clinical practice of administering a bolus followed by the steady-state infusion (Equation 3). It can be seen that the two-step infusion scheme significantly improves accuracy.

## Discussion

The hypothesis presented in this paper is that the target plasma concentration of an intravenously administered drug can be approximately maintained throughout a case by exactly achieving it at specific times. The algorithm used to implement this approach is based on the observation that the rate of an infusion needed to achieve the target plasma concentration $C_0$ at time t is equal to $C_0/AUC(t)$. This observation does not seem to have been discussed explicitly in the literature to date. The algorithm that derives from it appears to be effective, as judged by the simulation presented in this paper. Using a three-step infusion sequence, the maximum error for fentanyl was 38%, which is less than the variance in pharmacokinetic parameters or in the therapeutic windows for many anesthetic drugs.[6] The maximum error for midazolam was 10%. The maximum error for the fentanyl simulation was a transient phenomenon and rapidly decreased. It should be noted that the technique errs by underachieving the target concentration. The precision of the technique could be improved by increasing the number of infusions. However, this probably offers little clinical advantage, since the error intrinsically associated with the algorithm is less than the variance in

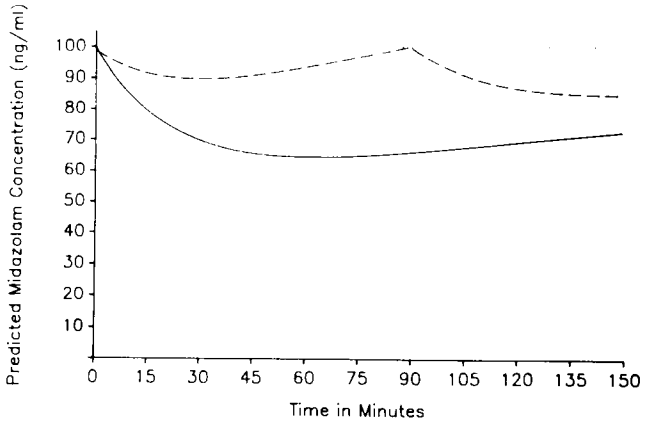


**Fig. 5. Plasma midazolam concentrations after a bolus dose of 44 μg/kg and an infusion of 0.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (solid line) or a bolus dose of 44 μg/kg with an infusion of 1.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (dashed line) reduced at 90 min to 0.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The dotted line indicates the target concentration of 100 ng/ml.**

the pharmacokinetic and pharmacodynamic parameters required for its implementation. The use of fewer infusions might be acceptable in many circumstances and more convenient to the busy anesthesiologist. Currently it is a common clinical practice to administer intravenous drugs by giving a bolus followed by the steady-state infusion of equation 3. Simply by adding one additional stage to the infusion scheme, accuracy is significantly improved, as illustrated in figure 5. The calculation necessary to determine the rate of the infusion (equations 1, 4, and 5) is straightforward.

In this paper, the selection of the initial bolus dose has not been considered. For some drugs this would be selected to rapidly produce the desired plasma concentration and would be calculated as $C_0 \times V_1$ [the central volume, equal to $1/(A_1 + A_2 + A_3)$ in equation 4]. For other drugs a larger bolus dose might be indicated to rapidly produce the desired effect site concentration.[4] Calculation of an appropriate loading dose is difficult because measurements of central volume can be sensitive to the frequency and site of blood sampling. The practitioner usually must rely on clinical experience. Fortunately the algorithm can be used with any initial bolus dose the practitioner believes is clinically indicated. The only limitation is that, if the bolus dose significantly exceeds the value needed to achieve $C_0$, the $t_1$ must be large enough for the term $C_0-C_b(t)$ in equation 1 to be positive.

The idea of approximating an exponentially decreasing infusion with a series of constant-rate infusions the magnitudes of which decrease in a stepwise fashion is not new. Wagner described this approach in 1974.[7] However, his algorithm was specifically derived for drugs whose pharmacokinetics were described by two compartment models, and the sequence was limited to only two steps. Vaughn and Tucker generalized the equations of Kruger-Thiemer[1] and then demonstrated how the infusion of lidocaine with an exponentially declining rate, needed to maintain a constant plasma level, could be approximated by a three-step infusion.[8] To accomplish this the cumulative amount of lidocaine delivered by the exponential infusion was calculated at multiple times (>20), then plotted as a function of time, and finally visually approximated by linear segments. The numerical labor of this approach is significantly greater than that of the algorithm described in this paper. Riggs and Wong used the same approach to develop an infusion scheme for morphine, but they reduced the numerical labor by employing computer simulation.[9] This is obviously an efficient technique of widespread applicability. However, for the practitioner who does not possess either computer skills or the appropriate programs, the algorithm described in this paper is a viable alternative. One could argue that implementation of equations 1–6 is less labor-intensive than computer simulation approaches for those who are not computer-literate. An example of the required numerical calculations is presented in Appendix 2.

An alternate technique for calculating the infusion rates in a two-stage algorithm was described recently by this author.[10] This technique requires calculation of first and second moments of the unit disposition function. It is less general than the approach described in this paper because it can not be extended to more than a two-stage infusion.

The approach used in this paper is somewhat distinct from that of Vaughn and Tucker[8] and Riggs and Wong.[9] Rather than calculating the rate of infusion by equating it to the average for the exact solution, the present algorithm was developed by achieving the exact target at specific times. This may be advantageous in the clinical setting to the extent that the timing of specific events in the perioperative course (*e.g.*, intubation, incision, and intense dissection with the electric cautery) are predictable.

The parameters required for the implementation of this algorithm are the areas under the curve. Calculation of these parameters is facilitated by the use of polyexponential equations to describe the response to a bolus dose. However, the technique is model-independent, other than the assumption of linear kinetics. In particular, the use of specific models comprised of compartments with micro-rate constants is unnecessary. Furthermore, the assumption of a polyexponential equation for the unit dose-response function is not intrinsic to the algorithm (although it is convenient). This could prove to be helpful in the future since the use of alternative functions, based on Erlang transit times or gamma distributions, have been recommended by some investigators.[11,12] However, it should be noted that the infusion rates are guaranteed to be positive only for a monotonically decreasing unit dose-response such as the polyexponential function.

In principle, AUC(t) could be calculated by numerical integration of raw bolus data. However, this data is rarely published and this is not a practical approach. Furthermore, using a model such as a polyexponential function smooths the data, eliminating some random noise, and it is not certain what the effects of random noise, such as drug assay error, would be if raw kinetic

data were numerically integrated. In calculating AUC(t) using the polyexponential model, average values for $A_1$, $A_2$, $A_3$, $k_1$, $k_2$, and $k_3$ have been used. However, it is not clear whether it would be more correct to calculate AUC(t) for individual patients and then average the results or to calculate AUC(t) from average concentrations. This is a complex statistical issue that needs further investigation since model-independent parameters are increasingly being used in the pharmacokinetic literature.[3]

It is worthwhile to note an interesting theoretical implication of this approach. Pharmacokinetic parameters are often determined by giving a single dose and then following the plasma concentration as a function of time after the dose. However, the anesthesiologist might well question the relevance of concentrations measured many hours after a bolus dose to the clinical use of the drug in cases that last only a few hours. The equations developed in this paper confirm that this information is irrelevant. Equation A10 becomes exact in the limit of increasing number of n (the number of steps in the sequence of infusions). Yet equation A10 reveals that the infusion is determined by parameters of the form AUC($\tau$), where $\tau$ is less than or equal to the duration of the case. The information found in the single dose-response curve at longer times is not needed. There is a parallel between this observation and other recent investigations that demonstrate that terminal phase kinetics, *i.e.*, long-time data, do not have a clinically significant impact on the use of many agents employed for intravenous anesthesia.[4,5]

It is sometimes noted that "model-independent" approaches to pharmacokinetics are not strictly model-independent, since parameters such as AUC($\infty$) require extrapolation of the single dose *versus* concentration in time curve and this, of necessity, implies a model.[3] The use of the truncated area under the curve AUC(t) avoids this problem. There is an intuitively satisfying parallel between (1) the often noted observation that a given plasma concentration $C_0$ will be asymptotically established (which strictly means after an infinite time) by an infusion at a rate equal to $C_0/AUC(\infty)$ and (2) the observation of this paper that the same plasma concentration can be achieved at some time t (earlier than infinity!) by an infusion whose rate is $C_0/AUC(t)$.

## Appendix 1

Consideration is restricted to drugs with linear kinetics for which the plasma concentration as a function of time is given by

$$C(t) = \int_0^t I(\tau)R(t - \tau)d\tau \qquad (A1)$$

where I(t) is the rate of intravenous drug administration and R(t) is the plasma concentration, as a function of time, that results from the administration of a single dose of unit magnitude. This equation is best appreciated by noting that a continuous infusion can be approximated as a series of small bolus doses. The concentration at time t due to a bolus at some earlier time $\tau$ is equal to the magnitude of the bolus, $I(\tau)$, multiplied by $R(t - \tau)$, the unit dose-response function, evaluated for $t - \tau$ (since $t - \tau$ time units elapse between the time of the bolus dose and the time the concentration is measured). For linear kinetics, the concentration at time t is the sum of the contributions from each bolus in the history of the infusion. This is evaluated by integrating $I(\tau)R(t - \tau)$ over $\tau$.

If the rate of infusion has a constant value $I_1$, then the above equation can be simplified to

$$C(t) = I_1 \int_0^t R(t - \tau)d\tau. \qquad (A2)$$

The equation can be rewritten by letting $x = t - \tau$ so that $d\tau = -dx$ with integration limits for x of t and 0. Hence

$$C(t) = I_1 \int_0^t R(x)dx = I_1AUC(t), \qquad (A3)$$

where I have denoted the integration of R from zero to time t as AUC(t) (for area under the curve to time t). Please note that this term differs from the commonly employed parameter of area under the curve in that it is divided by dose.

By inverting the above equation, it is seen that to achieve a given concentration $C_0$ at time t using a single constant-rate infusion the rate of this infusion, $I_1$ should be equal to $C_0/AUC(t)$.

Consider a slightly more complicated infusion scheme with an infusion of constant-rate $I_1$ from time zero to time equal to $t_1$ and then a second infusion of constant-rate $I_2$ from that point on. It will be assumed that $I_1$ is equal to the value needed to achieve the target plasma concentration of $C_0$ at $t_1$ derived above. Then the concentration at a time after the infusion rate has been changed to $I_2$ is given by

$$C(t) = I_1 \int_0^{t_1} R(t - \tau)d\tau + I_2 \int_{t_1}^t R(t - \tau)d\tau, \qquad (A4)$$

where

$$I_1 = \frac{C_0}{AUC(t_1)}. \qquad (A5)$$

This equation also can be simplified by letting $x = t - \tau$ and $d\tau = -dx$ and changing the limits of integration appropriately

$$C(t) = I_1 \int_{t-t_1}^t R(x)dx + I_2 \int_0^{t-t_1} R(x)dx. \qquad (A6)$$

We note that

$$\int_{t-t_1}^t R(x)dx = \int_0^t R(x)dx - \int_0^{t-t_1} R(x)dx. \qquad (A7)$$

and conclude

$$C(t) = I_1[AUC(t) - AUC(t - t_1)] + I_2AUC(t - t_1). \quad (A8)$$

Thus for the concentration C(t) to equal $C_0$ at some time $t_2$ (where $t_2 > t_1$) the infusion rate $I_2$ must be equal to

$$I_2 = \frac{C_0 - I_1[AUC(t_2) - AUC(t_2 - t_1)]}{AUC(t_2 - t_1)} \quad (A9)$$

This approach can be generalized readily to a dosage scheme consisting of an initial bolus with n sequential infusions of stepwise decreasing rate. The effect of the initial bolus is taken into account by simply subtracting $C_b(t)$, where $C_b(t)$ is the concentration at time t due to the initial bolus of magnitude B, from $C_0$. The rate of the nth infusion is given by the following equation.

$$I_n = \frac{C_0 - C_b(t) - \sum_{i=1}^{n-1} I_i[AUC(t_n - t_{i-1}) - AUC(t_n - t_i)]}{AUC(t_n - t_{n-1})} \quad (A10)$$

This equation is implemented by first setting n = 1 and determining the value of $I_1$ after noting that the second term in the numerator is identically zero for n = 1. Next, set n = 2 in the equation and use the previously determined value of $I_1$ to evaluate $I_2$. Higher order terms are evaluated by continuing this iterative approach.

The approach used to derive equation A10 is similar to a numerical deconvolution technique described by Verotta,[14] although the AUC(t) parameters were not explicitly identified by Verotta, nor was the issue of maintaining constant plasma levels explicitly addressed.

## Appendix 2

The actual numerical calculations required for implementation of this algorithm can be illustrated further with an example. Consider the infusion of amrinone for inotropic support after cardiac surgery. A study of patients with chronic congestive heart failure has demonstrated that a plasma concentration of 2.5 μg/ml is associated with a significant increase in cardiac output[15]; it is extrapolated here to cardiac surgical patients, and this value is considered the target plasma concentration. A bolus dose will be given to achieve this concentration, and an infusion is begun simultaneously to generate this same concentration after 30 min, an interval that could be viewed as a sufficient period to assess the effects of the drug. Thus $t_1$ is equal to 30 min. $t_2$ will be assigned a value consistent with the anticipated time to completion of the surgery, for example, 90 min. (Note that the selection of $t_1$ and $t_2$ is somewhat arbitrary but should, in general, be a reflection of the specific role of the drug in the surgical procedure). Referring to equations 1, 2, and 3, the parameters needed for calculation of the infusion rates are

$$AUC(t_1) = AUC(30)$$

$$AUC(t_2 - t_1) = AUC(90 - 30) = AUC(60)$$

$$AUC(t_2) = AUC(90)$$

$$AUC(\infty)$$

$$C_b(t_1) = C_b(30)$$

$$C_b(t_2) = C_b(90).$$

Referring to table 5 of reference 15 for pharmacokinetic parameters, note that the plasma concentration (in μg/ml) resulting from a bolus dose of 1 mg/kg is given by

$$C_b(t) = 6.02 \times e^{(-0.253 \cdot t)} + 1.4 \times e^{(-0.00499 \cdot t)}$$

To achieve a plasma concentration of 2.5 μg/ml a bolus dose of

$$2.5/(6.02 + 1.4) = 0.34 \text{ mg/kg},$$

is needed.

The concentrations that result from a bolus dose of 0.34 mg/kg at 30 and 90 min are given by

$$C_b(30) = 0.34 \times [6.02 \times e^{(-0.253 \cdot 30)} + 1.4 \times e^{(-0.00499 \cdot 30)}]$$

$$C_b(30) = 0.41$$

$$C_b(90) = 0.34 \times [6.02 \times e^{(-0.253 \cdot 90)} + 1.4 \times e^{(-0.00499 \cdot 90)}]$$

$$C_b(90) = 0.30$$

The areas under the curve are calculated from equations 5 and 6 (setting $A_1$ equal to zero since amrinone kinetics are described by a two-compartment model).

$$AUC(30) = (6.02/0.253) \times [1 - e^{(-0.253 \cdot 30)}] + (1.4/0.00499) \times [1 - e^{(-0.00499 \cdot 30)}]$$

$$AUC(30) = 62.8 \text{ (units are } \mu g \cdot min^{-1} \cdot kg^{-1}/ml \cdot mg^{-1})$$

$$AUC(60) = (6.02/0.253) \times [1 - e^{(-0.253 \cdot 60)}] + (1.4/0.00499) \times [1 - e^{(-0.00499 \cdot 60)}]$$

$$AUC(60) = 96.4$$

$$AUC(90) = (6.02/0.253) \times [1 - e^{(-0.253 \cdot 90)}] + (1.4/0.00499) \times [1 - e^{(-0.00499 \cdot 90)}]$$

$$AUC(90) = 125.3$$

$$AUC(\infty) = (6.02/0.253) + (1.4/0.00499) = 304.4.$$

Now the infusion rates can be calculated. Using equation 1,

$$I_1 = (2.5 - 0.41)/62.8 = 0.0333 \text{ mg} \cdot kg^{-1} \cdot min^{-1} = 33.3 \text{ μg} \cdot kg^{-1} \cdot min^{-1}.$$

Using equation 2,

$$I_2 = [2.5 - 0.3 - 0.0333 \times (125.3 - 96.4)]/96.4 = .0128 \text{ mg} \cdot kg^{-1} \cdot min^{-1} = 12.8 \text{ μg} \cdot kg^{-1} \cdot min^{-1}.$$

Using equation 3,

$$I_3 = 2.5/304.4 = 0.0082 \text{ mg} \cdot kg^{-1} \cdot min^{-1} = 8.2 \text{ μg} \cdot kg^{-1} \cdot min^{-1}.$$

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