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Rapid Attainment of Successively Higher Steady-State Plasma Levels Using the Wagner Two-Step Infusion Method

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Abstract □ The Wagner equation describing the plasma concentration–time relationship for the two-step infusion method is presented in general form for application to both the fast and slow infusion phases of single- and multiple-cycle infusions. The generalized parameters C (steady-state concentration), Q (infusion rate), A (amount of drug), and t' (time) are defined for each case. Plasma concentrations are simulated for a hypothetical two-compartment drug, X, to illustrate the uses of the equation and to examine error effects in the Q^F/Q^S ratio, T, and k_{e1}. For the single-cycle case, it is shown that positive or negative (±) errors in Q^F/Q^S and T delay the approach to the steady-state plasma value, C_1^{ss}, but such errors would not be of clinical importance when they are $\leq \pm 2.5\%$. Errors in k_{e1} prevent attainment of C_1^{ss} and more greatly affect the plasma concentration at the end of the dose cycle, $C_1^{\prime}$, than do the same errors in Q^F/Q^S or T. Therefore, the use of an average population value for k_{e1} instead of the actual patient value is more likely to produce large deviations from C_1^{ss} than experimental errors in flow rate and T. The utility of the two-step infusion method in reaching successively higher steady-state values, $C_{1,(n)}^{ss}$, for drugs with a high therapeutic index is also demonstrated for drug X over a range of multiple cycles. The examination of error effects for the multiple-cycle case revealed that errors in Q^F/Q^S and T yield $C_{1,(n)}^{\prime}$ values that tend to converge toward the desired value of $C_{1,(n)}^{ss}$ as the dose cycle increases, while such errors in k_{e1} yield $C_{1,(n)}^{\prime}$ values that increasingly diverge from $C_{1,(n)}^{ss}$ as dosing increases. Thus, individual patient differences as reflected in k_{e1} become increasingly more important as a source of error in $C_{1,(n)}^{\prime}$ with successively higher dosing, while experimental errors in Q^F/Q^S become less important.

Keyphrases □ Plasma levels—successively higher at steady state, obtained using two-step infusion method, simulated data for hypothetical drug □ Infusion methods, two step—used to obtain successively higher plasma levels at steady state, simulated data for hypothetical drug □ Pharmacokinetics—successively higher plasma levels at steady state obtained using two-step infusion method, simulated data for hypothetical drug

Methods for reducing the characteristic slow approach to steady state for drugs administered by infusion include: A, an initial intravenous (1, 2) or intramuscular (3) loading dose followed by a constant rate infusion; B, a two-step infusion process using two consecutive constant rate infusions (4, 5); and C, an initial intravenous loading dose followed by a real or simulated exponential infusion (6).

The loading dose methods (A) have the disadvantage of exhibiting a large early overshoot component in reaching the steady state (2) or mimicking the usual infusion process by eventually exhibiting a slow approach to the steady state (1, 3). These disadvantages are potentially minimized by Methods B and C. Method C (6), however, is difficult to employ since it requires either a special pump capable of exponential delivery or a series of consecutive constant rate infusions to simulate an exponential input.

The two-step infusion method of Wagner (4) appears to be the most ideal, because of its relative ease of employment and potential for producing a rapid steady state. While an overshoot component is associated with the two-step infusion method, the degree of overshoot can be predetermined and, therefore, controlled.

The purpose of this report is to expand upon the Wagner method to demonstrate its utility in attaining successively higher steady-state plasma levels for cases where a drug must be given at successively higher doses to achieve continued therapeutic response. The effect of error in key pharmacokinetic parameters on the simulated plasma concentrations is also examined.

THEORETICAL

Use of the two-step infusion method requires that an initial fast infusion rate, Q^F, be employed for a time interval, T, after which the infusion rate is immediately reduced to a slower infusion rate, Q^S, to attain and maintain the desired steady-state plasma level. At T, the plasma concentration, C_1^{max}, will be greater than the steady-state plasma level, C_1^{ss}, producing the overshoot component mentioned. The relative overshoot, C_1^{max}/C_1^{ss}, defined by Eq. 1 (4) is dependent on T and the kinetic constants α, β, and k_{e1} for a two-compartment drug (7):

$$\frac{C_1^{max}}{C_1^{ss}} = \frac{1}{1-e^{-\beta T}}\left[1 - \left\{\frac{k_{e1}-\beta}{\alpha-\beta}\right\}e^{-\alpha T} - \left\{\frac{\alpha-k_{e1}}{\alpha-\beta}\right\}e^{-\beta T}\right] \quad \text{(Eq. 1)}$$

Any degree of overshoot can be selected, depending on the choice of T.

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In general, the larger T is, the smaller is the overshoot. The required value of T can be obtained by inserting the values of α, β, and k_{e1} into Eq. 1 and subsequently varying T to obtain the desired relative overshoot.

The plasma concentration, C_1, of a two-compartment drug administered by the two-step infusion method is expressed in general form by:

$$C_1 = C + \left\{\frac{(k_{21}-\alpha)(Q-\alpha A_1)-\alpha k_{21}A_2}{\alpha(\alpha-\beta)V_1}\right\} e^{-\alpha t'} - \left\{\frac{(k_{21}-\beta)(Q-\beta A_1)-\beta k_{21}A_2}{\beta(\alpha-\beta)V_1}\right\} e^{-\beta t'} \quad \text{(Eq. 2)}$$

where subscripts 1 and 2 refer to the central and peripheral compartments, respectively; A represents the amount of drug in the respective compartments; and Q represents either Q^F or Q^S, depending on whether the concentration being calculated is that of the fast or slow infusion phase. The values of C, Q, A, and t' are defined differently within the fast and slow phases of single- and multiple-cycle cases.

Single Cycle—*Fast Phase*—Within the fast phase of a single cycle, the value of C in Eq. 2 becomes $C_1^{ss'}$ (Eq. 3), the hypothetical plasma concentration that results if the fast infusion rate, Q^F, is allowed to proceed to steady state:

$$C_1^{ss'} = Q^F/V_1k_{e1} \quad \text{(Eq. 3)}$$

where Q^F is given by (4):

$$Q^F = Q^S/(1-e^{-\beta T}) \quad \text{(Eq. 4)}$$

and Q^S is defined by:

$$Q^S = C_1^{ss}V_1k_{e1} \quad \text{(Eq. 5)}$$

where C_1^{ss} is the desired steady-state plasma concentration. Furthermore, t' assumes values from $0 \rightarrow T$, and the constants A_1 and $A_2 = 0$.

Slow Phase—Within the slow phase of a single cycle, the value of C in Eq. 2 becomes C_1^{ss}, Q is substituted by Q^S (Eq. 5), and t' is given by:

$$t' = t - T \quad \text{(Eq. 6)}$$

where t is the continuous time period within the fast–slow infusion cycle and T is the required value calculated from Eq. 1. The values of A_1 and A_2 are equal to A_1^T (Eq. 7) and A_2^T (Eq. 8), respectively (4):

$$A_1^T = \frac{Q^F}{k_{e1}} + \left\{\frac{Q^F(k_{21}-\alpha)}{\alpha(\alpha-\beta)}\right\} e^{-\alpha T} - \left\{\frac{Q^F(k_{21}-\beta)}{\beta(\alpha-\beta)}\right\} e^{-\beta T} \quad \text{(Eq. 7)}$$

$$A_2^T = \frac{k_{12}Q^F}{k_{21}k_{e1}} + \left\{\frac{k_{12}Q^F}{\alpha(\alpha-\beta)}\right\} e^{-\alpha T} - \left\{\frac{k_{12}Q^F}{\beta(\alpha-\beta)}\right\} e^{-\beta T} \quad \text{(Eq. 8)}$$

where the superscript T indicates that the quantities calculated are for amounts of drug in the respective compartments at the end of the fast infusion phase.

Multiple Cycles—The expressions given apply to cycles initiated after a steady-state plasma level is established for any given cycle.

Fast Phase—Within the fast phase of the nth infusion cycle, the value of C in Eq. 2 is equal to $C_{1,(n)}^{ss'}$ as given by:

$$C_{1,(n)}^{ss'} = Q_{(n)}^F/V_1k_{e1} \quad \text{(Eq. 9)}$$

where the subscript (n) refers to the cycle number and $Q_{(n)}^F$ is the fast infusion rate for cycle n defined by:

$$Q_{(n)}^F = Q_{(1)}^F + Q_{(n-1)}^S \quad \text{(Eq. 10)}$$

where $Q_{(1)}^F$ is the fast infusion rate for cycle 1 and $Q_{(n-1)}^S$ is the slow infusion rate for cycle $(n-1)$ defined by:

$$Q_{(n-1)}^S = C_{1,(n-1)}^{ss}V_1k_{e1} \quad \text{(Eq. 11}a\text{)}$$

Equation 11a reduces to Eq. 11b when the steady-state concentration is increased by constant increments:

$$Q_{(n-1)}^S = (n-1)Q_{(1)}^S \quad \text{(Eq. 11}b\text{)}$$

where $Q_{(1)}^S$ is the slow infusion rate for cycle 1.

Within cycles, t' assumes values from $0 \rightarrow T$; but when cycles are initiated at constant time intervals, t' is generalized by:

$$t' = t - (n-1)\tau \quad \text{(Eq. 12)}$$

where t is the continuous time period from time zero, t' is the time within any given cycle, and τ is the length of each cycle.

Corresponding values of A_1 and A_2 at the beginning of the fast phase are equal to $A_{1,(n-1)}^{ss}$ (Eq. 13) and $A_{2,(n-1)}^{ss}$ (Eq. 14), respectively:

$$A_{1,(n-1)}^{ss} = Q_{(n-1)}^S/k_{e1} \quad \text{(Eq. 13)}$$

$$A_{2,(n-1)}^{ss} = k_{12}Q_{(n-1)}^S/k_{21}k_{e1} \quad \text{(Eq. 14)}$$

By definition, the value of $Q_{(n-1)}^S$ for cycle 1 equals zero, producing values of A_1 and A_2 in agreement with those set for the fast phase of the single-cycle case.

Slow Phase—In the slow phase of the nth infusion cycle, C in Eq. 2 is substituted by $C_{1,(n)}^{ss}$, which represents the desired steady-state plasma level for cycle n. The parameter Q is defined by:

$$Q_{(n)}^S = C_{1,(n)}^{ss}V_1k_{e1} \quad \text{(Eq. 15}a\text{)}$$

Equation 15a reduces to Eq. 15b when the steady-state plasma concentration is increased by constant increments:

$$Q_{(n)}^S = (n)Q_{(1)}^S \quad \text{(Eq. 15}b\text{)}$$

The parameter t' assumes values from $0 \rightarrow (\tau - T)$ within any given cycle; but when cycles are initiated at constant time intervals, t' is generalized by:

$$t' = t - (n-1)\tau - T \quad \text{(Eq. 16)}$$

Corresponding values of A_1 and A_2 at the beginning of the slow phase of the nth infusion cycle are equal to $A_{1,(n)}^{tot}$ (Eq. 17) and $A_{2,(n)}^{tot}$ (Eq. 18), respectively:

$$A_{1,(n)}^{tot} = A_{1,(n-1)}^{ss} + A_1^T \quad \text{(Eq. 17)}$$

$$A_{2,(n)}^{tot} = A_{2,(n-1)}^{ss} + A_2^T \quad \text{(Eq. 18)}$$

where A_1^T and A_2^T are calculated from Eqs. 7 and 8, respectively, using a Q value of $Q_{(1)}^F$.

RESULTS AND DISCUSSION

The applications of Eqs. 1–18 are demonstrated by use of the following pharmacokinetic constants for hypothetical drug X: $V_1 = 1.50$ liters/kg, $\alpha = 3.6\ hr^{-1}$, $\beta = 0.2\ hr^{-1}$, $k_{e1} = 0.6\ hr^{-1}$, $k_{12} = 2.0\ hr^{-1}$, and $k_{21} = 1.2\ hr^{-1}$. It is assumed that the drug has a usual therapeutic concentration of 0.60 μg/ml and a toxic level of 5.0 μg/ml in normal adults, thereby lending itself to use in multiple-cycle infusions.

Single-Cycle Case—Figure 1 illustrates the use of Eqs. 1–8 for the single-cycle case (error free) with variations in T where $C_1^{ss} = 0.60$ μg/ml. The corresponding value of $Q^S = 0.54$ mg/kg/hr; Q^F values were calculated from Eq. 4 using appropriate values of T. The T values of 0.5, 1, and 1.5 hr were selected for the simulations for which the corresponding relative overshoot values, C_1^{max}/C_1^{ss}, are 1.914, 1.514, and 1.334, respectively. The larger overshoot associated with the smaller T values is clearly visible in the figure.

A steady value of 0.60 μg/ml is easily reached for all three values of T within 3 hr. By contrast, the single-infusion method (lower curve, Q^S = 0.54 mg/kg/hr) after a dosing cycle of 4 hr produces a plasma level of only 0.604 C_1^{ss}, with 22.4 hr being required to reach 99% of the steady-state value.

Errors in Q^F *and* T—Rapid attainment of the steady state as shown in Fig. 1 is highly dependent on the correctness of the Q^F/Q^S ratio and the T value. Figures 2 and 3 demonstrate the effect of error in these two quantities relative to the time required to reach the steady state.

Figure 2 represents simulations for an extreme error of ±50% in the Q^F/Q^S ratio, achieved by varying Q^F while maintaining Q^S constant at 0.54 mg/kg/hr for $C_1^{ss} = 0.60$ μg/ml and $T = 1$ hr. The corresponding error-free value for $Q^F = 2.979$ mg/kg/hr, as calculated from Eq. 4. These simulations depict the effect of a ±50% error in Q^F used in Eqs. 2, 7, and 8 on the time required to reach a steady-state value of 0.60 μg/ml. When Q^F is reduced by 50% of its original value (lower curve), overshoot of the steady state does not occur, but approach to the steady state is very slow. Alternatively, when Q^F is increased by 50% of its original value (upper curve), there is a larger than normal overshoot of the steady state; the plasma level remains elevated above normal (middle curve) for an extended time, again producing a very slow approach to the steady state. At 4 hr, the plasma concentrations for +50 and −50% errors in Q^F are 1.242 C_1^{ss} and 0.758 C_1^{ss}, respectively.

Figure 3 represents simulations for an extreme error of ±50% in T based on an error-free value of $T = 1$ hr. The Q^F/Q^S is maintained constant using the error-free values for Q^F and Q^S at $C_1^{ss} = 0.60$ μg/ml.

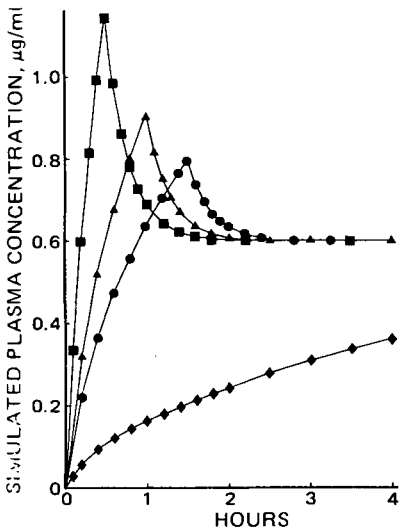

Figure 1—*Simulated plasma concentration–time curves for drug* X *comparing the two-step infusion method at* T *values of 0.5 (■), 1.0 (▲), and 1.5 (●) hr with the single-infusion rate method (♦). For all curves,* C_1^{ss} *= 0.60 μg/ml and* Q^S *= 0.54 mg/kg/hr.*

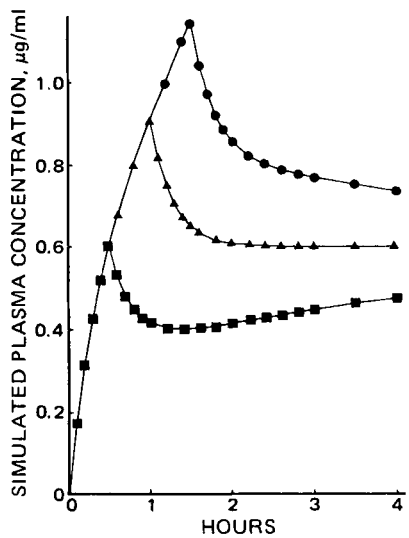

Figure 3—*Plasma concentration–time curves for drug* X *simulated by the two-step infusion method comparing the effects of −50% (■) and +50% (●) error in* T *with the error-free curve (▲). For all curves,* C_1^{ss} *= 0.60 μg/ml,* Q^S *= 0.54 mg/kg/hr, and* Q^F *= 2.979 mg/kg/hr.*

Qualitatively, the results of these simulations are completely analogous to those for Fig. 2; *i.e.*, a 50% reduction in T (lower curve) eliminates overshoot of the steady state while a 50% increase in T (upper curve) yields a larger than normal overshoot of the steady state followed by plasma levels that are elevated above normal (middle curve) for an extended period. The end result of both errors is a very slow approach to the steady state. The corresponding plasma concentrations at the end of the 4-hr dosing cycle for +50 and −50% errors in T are 1.230 $C_1^{ss}$and 0.792 C_1^{ss}, respectively.

In general, Figs. 2 and 3 show that the presence of error in the Q^F/Q^S ratio or the T value increases the time required to reach the steady state. This condition is further illustrated in Table I where the percent error in Q^F for drug X is compared with the time, t, required to reach 99% of the steady-state value. An error as small as 2.5% in Q^F increases the time required to reach 99% of steady state by a factor of approximately 2.5 times (*i.e.*, 4.96 hr *versus* 2.09 hr). Larger errors even more greatly extend the time required to reach 99% of the steady-state value. An analogous table based on the percent error in T yields very similar values of t.

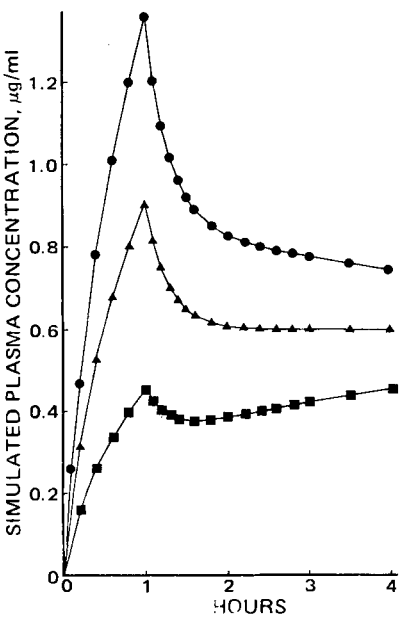

Figure 2—*Plasma concentration–time curves for drug* X *simulated by the two-step infusion method comparing the effects of −50% (■) and +50% (●) error in* Q^F *with the error-free curve (▲). For all curves,* C_1^{ss} = 0.60 μg/ml, Q^S *= 0.54 mg/kg/hr, and* T = *1 hr.*

Table II summarizes the error effects in Q^F and T at intermediate values within the ±50% error range. Errors in plasma concentrations are tabulated as $\%C_1^{max}$ (*i.e.*, percent of error-free concentration at the end of the fast infusion phase) and $\%C_1^{\tau}$ (*i.e.*, percent of error-free concentration at the end of the 4-hr dosing cycle). In contrast to the large displacements of the concentration–time profiles in Figs. 2 and 3 for ±50% errors, it is apparent from Table II that relatively small errors in Q^F and T of approximately ±2.5% will have only minor effects on C_1^{max} and C_1^{τ} after a single cycle. Therefore, errors in Q^F and T would not be expected to affect greatly the peak and steady-state plasma levels in well-controlled clinical studies.

Errors in k_{el} *and* β—Rapid attainment of the steady state using the two-step infusion method largely depends on an accurate assessment of the pharmacokinetic constants V_1, α, β, and k_{e1} used in Eqs. 1–5. Often, however, infusion therapy may be initiated using average population values for these constants instead of actual patient values. In this case, the patient may never exhibit plasma levels corresponding to C_1^{ss} even when Q^F, Q^S, and T are error free.

While intersubject variation is expected to exist for any of the pharmacokinetic parameters of a two-compartment drug, the greatest variability is often seen in the elimination rate constant, k_{e1}. Figure 4 was constructed to demonstrate the effect of error in k_{e1} in preventing attainment of C_1^{ss}. The simulations in Fig. 4 represent ±50% errors in k_{e1}, with concomitant changes in α and β calculated according to Eqs. 19 and 20 (7), respectively:

$$\alpha = \tfrac{1}{2}\left[(k_{12} + k_{21} + k_{e1}) + \sqrt{(k_{12} + k_{21} + k_{e1})^2 - 4k_{21}k_{e1}}\right] \quad \text{(Eq. 19)}$$

$$\beta = \tfrac{1}{2}\left[(k_{12} + k_{21} + k_{e1}) - \sqrt{(k_{12} + k_{21} + k_{e1})^2 - 4k_{21}k_{e1}}\right] \quad \text{(Eq. 20)}$$

Table I—Effect of Error in Q^F on the Time Required to Reach 99% of Steady State [a]

Error in Q^F, ±%	t, hr [b]
0	2.09
1.0	2.40
2.5	4.96
5.0	8.43
10.0	11.89
25.0	16.47
50.0	19.94

[a] Calculated by varying Q^F while maintaining Q^S constant at 0.54 mg/kg/hr for C_1^{ss} = 0.60 μg/ml and T = 1 hr. The error-free value of Q^F = 2.979 mg/kg/hr. [b] t = time required to reach 99% of the steady-state value.

Table II—Values [a] of $\%C_1^{max}$ and $\%C_1^{\tau}$ as a Function of Error in Q^F and T for the Single-Cycle Case [b]

Error, %	Q^F		T	
	$\%C_1^{max}$	$\%C_1^{\tau}$	$\%C_1^{max}$	$\%C_1^{\tau}$
+50.0	150.0	124.2	126.0	123.0
+25.0	125.0	112.1	113.5	111.2
+10.0	110.0	104.9	105.6	104.4
+5.0	105.0	102.4	102.8	102.2
+2.5	102.5	101.2	101.4	101.1
0	100.0	100.0	100.0	100.0
−2.5	97.5	98.8	98.6	98.9
−5.0	95.0	97.6	97.1	97.8
−10.0	90.0	95.2	94.2	95.7
−25.0	75.0	87.9	84.8	89.3
−50.0	50.0	75.8	66.4	79.2

[a] $\%C_1^{max}$ = percent of error-free concentration at the end of the fast infusion cycle; $\%C_1^{\tau}$ = percent of error-free concentration at the end of the 4-hr dosing cycle. [b] The C_1^{max} and C_1^{τ} values as a function of error in Q^F and T were calculated for the respective conditions given in Figs. 2 and 3. The 100% values for $\%C_1^{max}$ and $\%C_1^{\tau}$ correspond to C_1^{max} = 0.9082 μg/ml and C_1^{τ} = 0.60 μg/ml, respectively.

Table III—Values [a] of $\%C_1^{max}$ and $\%C_1^{\tau}$ as a Function of Error in k_{e1} and β for the Single-Cycle Case [b]

Error in k_{e1}, %	Error[c] in β, %	$\%C_1^{max}$	$\%C_1^{\tau}$
+90	+71.1	84.6	61.5
+70	+56.7	87.6	67.8
+50	+41.5	90.9	75.1
+30	+25.5	94.4	83.8
+10	+8.7	98.1	94.1
0	0	100.0	100.0
−10	−8.9	102.0	106.4
−30	−27.5	106.2	121.2
−50	−47.0	110.6	139.1
−70	−67.4	115.3	160.9
−90	−88.9	120.3	187.7

[a] See footnote *a* of Table II. [b] The C_1^{max} and C_1^{τ} values as a function of error in k_{e1} were calculated for the conditions given in Fig. 4. The 100% values of $\%C_1^{max}$ and $\%C_1^{\tau}$ correspond to C_1^{max} = 0.9082 μg/ml and C_1^{τ} = 0.60 μg/ml, respectively. [c] The β values as a function of error in k_{e1} were calculated from Eq. 20.

The constants k_{12}, k_{21}, and V_1 were assumed to be error free; Q^S and Q^F were assumed to be error free for the conditions of C_1^{ss} = 0.60 μg/ml and T = 1 hr. The ±50% errors in k_{e1} correspond to +41.5 and −47% errors in β and +5.7 and −6% errors in α. The calculated values (after rounding off) of α, β, and k_{e1} used in the simulations for a +50% error in k_{e1} were 3.187, 0.2829, and 0.9 hr^{-1}, respectively. For a −50% error in k_{e1}, the values of these constants were 3.394, 0.1061, and 0.3 hr^{-1}, respectively.

Because of the imposed errors in k_{e1}, the simulated upper and lower curves in Fig. 4 converge upon new steady-state values in accordance with Eq. 5. Thus, when k_{e1} is increased by 50% of its original value (lower curve), there is slight reduction in the normal overshoot value followed by a rapid drop in the plasma concentration below the desired value of C_1^{ss} = 0.60 μg/ml and then a gradual approach to a new steady-state value of 0.40 μg/ml. This simulation represents a hypothetical patient eliminating the drug more rapidly than the average patient.

When k_{e1} is decreased by 50% of its original value (upper curve), there is a slight increase in the normal overshoot value followed by a continued elevation above 0.60 μg/ml and then a gradual approach to a new steady-state value of 1.20 μg/ml. This simulation represents a slower-than-average eliminator of the drug. At 4 hr, the plasma concentrations for +50 and −50% errors in k_{e1} are 0.751 C_1^{ss} and 1.391 C_1^{ss}, respectively.

Table III summarizes the error effects in k_{e1} over a ± 90% error range. In addition to providing a tabulation of $\%C_1^{max}$ and $\%C_1^{\tau}$ values, Table III also gives corresponding percent errors in β for any given percent error in k_{e1}. A comparison of the error effects on C_1^{max} between Tables II and III shows that errors in k_{e1} have less influence on the peak concentration at the end of the fast infusion phase than do errors in Q^F and T. For example, a +50% error in k_{e1} and corresponding −50% errors in Q^F and T yield $\%C_1^{max}$ values of 90.9, 50, and 66.4%, respectively, while a −50% error in k_{e1} and corresponding +50% errors in Q^F and T yield $\%C_1^{max}$ values of 110.6, 150, and 126%, respectively. Relatively small errors in k_{e1} of ±10% yield errors in C_1^{max} of only 2%.

In contrast, however, negative errors in k_{e1} have a more pronounced effect on C_1^{τ}, the plasma concentration at the end of the dosing cycle, than corresponding errors in Q^F and T. For example, a −50% error in k_{e1} and corresponding +50% errors in Q^F and T yield $\%C_1^{\tau}$ values of 139.1, 124.2, and 123%, respectively. For a +50% error in k_{e1}, the resulting $\%C_1^{\tau}$ values are very similar to the −50% errors in Q^F and T (*i.e.*, 75.1, 75.8, and 79.2%, respectively).

For the extreme range of + and −90% errors in k_{e1}, the resulting $\%C_1^{\tau}$ values are 61.5 and 187.7%, respectively (Table III). Since it is not unlikely to find such a range of actual patient values that deviate from the average literature value in any clinical study, actual patient values may need to be determined, *a priori*, to avoid potential subtherapeutic or toxic plasma concentrations.

Multiple-Cycle Case—The applications of Eqs. 2 and 7–18 for the multiple-cycle case (error-free) are illustrated in Fig. 5 for the conditions $C_{1,(1)}^{ss}$ = 0.60 μg/ml and T = 1 hr. Accordingly, $Q_{(1)}^S$ = 0.54 mg/kg/hr and $Q_{(1)}^F$ = 2.979 mg/kg/hr. The values of Q required in Eq. 2 for the various cycles were calculated using Eqs. 10, 11*b*, and 15*b*, assuming equal doses and dosing intervals. Thus, for the third cycle: $Q_{(3)}^F = Q_{(1)}^F + (n-1)Q_{(1)}^S$ = [2.979 + 2(0.54)] mg/kg/hr = 4.059 mg/kg/hr and $Q_{(3)}^S = nQ_{(1)}^S$ = 3 (0.54) mg/kg/hr = 1.62 mg/kg/hr.

Drug X is depicted as having a usual therapeutic level of 0.60 μg/ml and a toxic level of 5 μg/ml, thereby possessing the property of a drug with a high therapeutic index. This property safely permits the use of successively higher plasma concentrations to achieve and maintain a continued therapeutic response. Seven cycles are simulated in Fig. 5 at a regular dosing interval of τ = 4 hr. All $C_{1,(n)}^{max}$ values fall safely within the therapeutic region, including the value for cycle 7 for which $C_{1,(7)}^{max}$ = 4.508 μg/ml.

The value of τ = 4 hr in Fig. 5 was selected for convenience in display purposes only since the dosing cycles could actually be initiated at any time following attainment of the steady state. Thus, for drug X, successive cycles may be as short as 2.5 hr, at which time C_1 is within 0.2% of

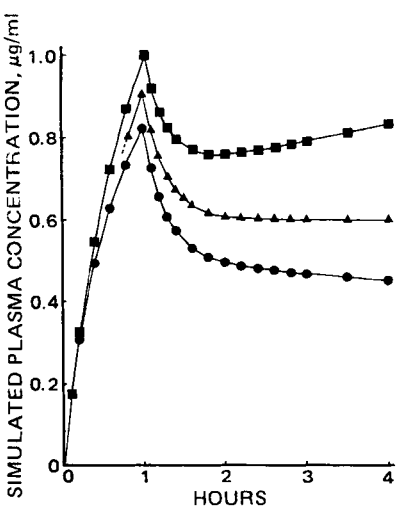

Figure 4—*Plasma concentration–time curves for drug* X *simulated by the two-step infusion method comparing the effects of −50% (■) and +50% (●) error in* k_{el} *with the error-free curve (▲). For all curves,* Q^S *= 0.54 mg/kg/hr,* T *= 1 hr, and* Q^F *= 2.979 mg/kg/hr.*

Table IV—Values [a] of $\%C_{1,(n)}^{\tau}$ as a Function of Various Error Conditions for the Multiple-Cycle Case [b]

Error Condition	Dose Cycle (n)		
	1	3	6
+50% k_{e1}	75.1	70.7	68.7
−50% Q^F	75.8	86.7	92.7
−50% T	79.2	88.5	93.8
0	100.0	100.0	100.0
+50% T	123.0	112.7	106.9
+50% Q^F	124.2	113.3	107.3
−50% k_{e1}	139.1	157.7	173.0

[a] $\%C_{1,(n)}^{\tau}$ = percent of error-free concentration at the end of the 4-hr dose cycle for the specified cycle, (n). [b] The $C_{1,(1)}^{\tau}$ values as a function of error in Q^F, T, and k_{e1} were calculated for the respective conditions given in Figs. 2–4. The 100% values of $\%C_{1,(n)}^{\tau}$ for cycles 1, 3, and 6 correspond to 0.6, 1.8, and 3.6 μg/ml, respectively.

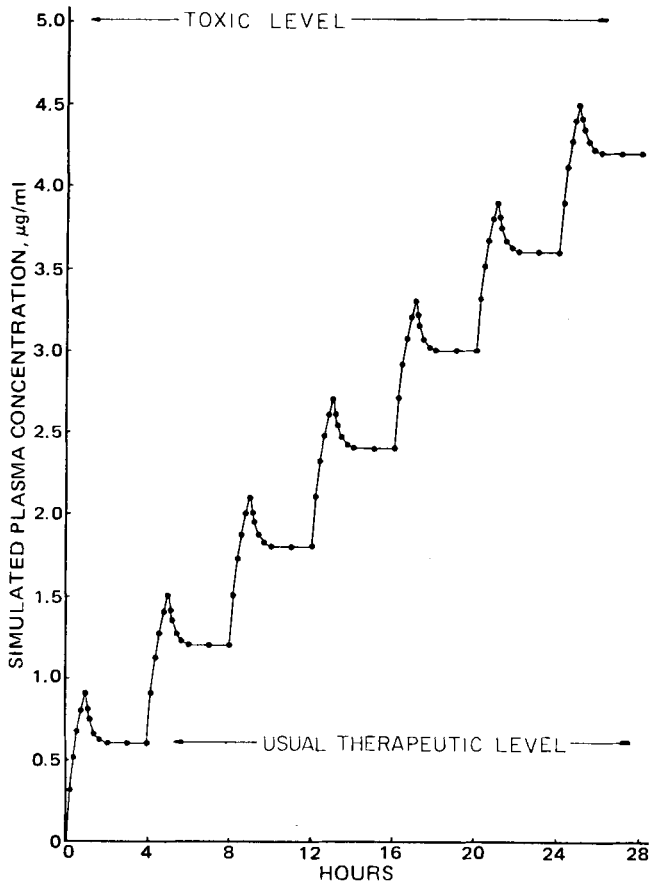

Figure 5—*Plasma concentration–time curves for drug* X *simulated by the two-step infusion method for the multiple-cycle case with* $C^{ss}_{1,(1)}$ = *0.60 μg/ml,* $Q^S_{(1)}$ = *0.54 mg/kg/hr,* T = *1 hr,* $Q^F_{(1)}$ = *2.979 mg/kg/hr, and* τ = *4 hr.*

$C^{ss}_{1,(n)}$, or longer than 4 hr, depending on the therapeutic need. Furthermore, the dosing cycles need not be spaced at regular intervals but may be sporadic, again depending on the therapeutic need.

Errors in Q^F, T, *and* k_{el}—Tables IV–VI summarize the errors in $C^{\tau}_{1,(n)}$, $C^{max}_{1,(n)}$, and $AUC|^{\tau}_{0,(n)}$ for six successively higher doses during 24 hr (*i.e.*, one dosing cycle every 4 hr) under various conditions. The conditions of ±50% error in Q^F, T, and k_{el} were used in these tables.

Since Eqs. 9–19 require that the steady state be attained prior to beginning the next dose, these equations could not be used for calculating the plasma concentrations required in compiling Tables IV–VI. Instead, the superposition principle was utilized (7). For each condition specified in these tables, the plasma concentrations for cycle 1 were computed with Eqs. 2–7 for specifically selected time intervals over 24 hr. The plasma concentrations of successive cycles were computed by simply stacking the cycle 1 data stepwise every 4 hr and summing the resulting concentration values at each point in time. The number of selected time intervals

Table V—Values[a] of $\%C^{max}_{1,(n)}$ as a Function of Various Error Conditions for the Multiple-Cycle Case[b]

Error Condition	Dose Cycle (*n*) 1	3	6
+50% k_{el}	90.9	79.5	73.7
−50% Q^F	50.0	70.3	83.0
−50% T	66.4	77.8	87.0
0	100.0	100.0	100.0
+50% T	126.0	118.2	110.7
+50% Q^F	150.0	129.7	117.0
−50% k_{el}	110.6	135.7	157.8

[a] $\%C^{max}_{1,(n)}$ = percent of error-free concentration at the end of the fast infusion phase for the specified cycle, (n). [b] The $C^{max}_{1,(n)}$ values as a function of error in Q^F, T, and k_{el} were calculated for the respective conditions given in Figs. 2–4. The 100% values of $\%C^{max}_{1,(n)}$ for cycles 1, 3, and 6 correspond to 0.9082, 2.1082, and 3.9082 μg/ml, respectively.

Table VI—Values[a] of $\%AUC|^{\tau}_{0,(n)}$ as a Function of Various Error Conditions for the Multiple-Cycle Case[b]

Error Condition	Dose Cycle (*n*) 1	3	6
+50% k_{el}	83.8	74.7	70.8
−50% Q^F	62.0	79.2	88.6
−50% T	70.4	83.1	90.7
0	100.0	100.0	100.0
+50% T	127.6	116.9	109.4
+50% Q^F	138.4	121.0	111.4
−50% k_{el}	122.9	146.8	166.0

[a] $\%AUC|^{\tau}_{0,(n)}$ = percent of error-free area under the curve from 0 → τ at the end of the 4-hr dose cycle for the specified cycle, (n). [b] The $AUC|^{\tau}_{0,(1)}$ values as a function of error in Q^F, T, and k_{el} were calculated for the respective conditions given in Figs. 2–4. The 100% values of $\%AUC|^{\tau}_{0,(n)}$ for cycles 1, 3, and 6 correspond to 2.4436, 7.2436, and 14.4436 μg hr/ml, respectively.

during each 4-hr cycle ranged between 8 and 12, depending on the specified condition. The same number of time intervals was used to calculate values of $AUC|^{\tau}_{0,(n)}$ by the trapezoidal rule for specified conditions.

Table IV gives $\%C^{\tau}_{1,(n)}$ values at the end of the slow infusion cycles during multiple dosing. Within any cycle, it is apparent that $\%C^{\tau}_{1,(n)}$ follows the order: +50% k_{el} < −50% Q^F < −50% T < EF < +50% T < +50% Q^F < −50% k_{el}, with extreme effects being imposed by ±50% errors in k_{el}. This order is not observed, however, for cycle 1 in Table V ($\%C^{max}_{1,(n)}$) or in Table VI ($\%AUC|^{\tau}_{0,(n)}$) where the extreme effects are imposed by ±50% errors in Q^F. Nevertheless, errors in k_{el} become increasingly important as the number of dosing cycles increases, and the order followed by $\%C^{\tau}_{1,(n)}$ is duplicated by $\%C^{max}_{1,(n)}$ and $\%AUC|^{\tau}_{0,(n)}$ beginning in dose cycles 5 and 3, respectively.

For ±50% errors in k_{el}, the calculated percentages, $\%C^{\tau}_{1,(n)}$, $\%C^{max}_{1,(n)}$, and $\%AUC|^{\tau}_{0,(n)}$, all increasingly diverge from 100% as the dosing cycle increases (Tables IV–VI). In contrast, for the conditions of ±50% errors

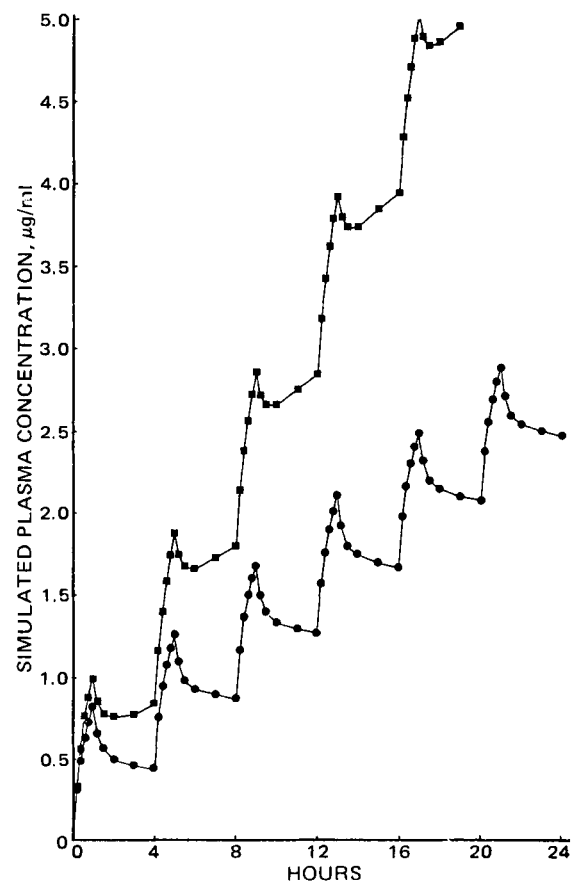

Figure 6—*Plasma concentration–time curves for drug* X *simulating the two-step infusion approach for the multiple-cycle case and comparing the effects of −50% (■) with +50% (●) error in* k_{el}. *For both curves,* $Q^S_{(1)}$ = *0.54 mg/kg/hr,* T = *1 hr, and* $Q^F_{(1)}$ = *2.979 mg/kg/hr.*

in Q^F and T, the calculated percentages all tend to converge toward 100% as dosing increases. For example, in the sixth dosing cycle of Table IV + and −50% errors in k_{el} yield $\%C^{\tau}_{1,(n)}$ values of 68.7 and 173%, respectively, while ±50% errors in Q^F and T produce $\%C^{\tau}_{1,(n)}$ values of 92.7–107.3%. Similar results are found in Tables V and VI for $\%C^{max}_{1,(n)}$ and $\%AUC|^{\tau}_{0,(n)}$, respectively.

The effect of ±50% errors in k_{el} during multiple-dose cycles is further illustrated in Fig. 6 for six successively higher doses over 24 hr. The shapes of the plasma profiles are obviously distorted when compared with the error-free profile in Fig. 5. The pronounced effect of a −50% error in k_{el} is evidenced by values of $C^{max}_{1,(n)}$ and $C^{\tau}_{1,(n)}$ that begin to exceed the hypothetical toxic level of 5 μg/ml after only five dose cycles. Values of $C^{max}_{1,(n)}$ and $C^{\tau}_{1,(n)}$ for a +50% error in k_{el} all safely fall within the therapeutic region over the total 24 hr as expected. The increasingly larger differences between the areas under the curve for ±50% errors in k_{el} as the dose cycle increases are immediately apparent.

It may be concluded that individual patient differences in elimination, as reflected in k_{el}, become increasingly more important as a source of error in $C^{max}_{1,(n)}$, $C^{\tau}_{1,(n)}$, and $AUC|^{\tau}_{0,(n)}$ with successively higher doses while experimental error in Q^F and T become less and less important.

Finally, it is cautioned that the attainment clinically of profiles as ideal as that in Fig. 5 depends on an accurate estimation of the pharmacokinetic parameters for the individual patient, a constancy in the values of the pharmacokinetic parameters during therapy, and careful administration of the drug with respect to both flow rate and T.

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Synthesis and Biological Activity of Cocaine Analogs I: *N*-Alkylated Norcocaine Derivatives

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Received January 30, 1978, from the **Section of Medicinal Chemistry and Pharmacognosy, School of Pharmacy, University of Connecticut, Storrs, CT 06268,* the ‡*Harvard Medical School New England Regional Primate Research Center, Southborough, MA 01772,* and the §*Department of Psychiatry, University of Chicago, Chicago, IL 60637.* Accepted for publication March 22, 1978.

Abstract □ *N*-Allylnorcocaine, *N*-dimethylallylnorcocaine, and *N*-cyclopropylmethylnorcocaine were prepared and examined for cocaine-like activity. The compounds were prepared by alkylation of norcocaine, which was obtained by demethylation of cocaine with 2,2,2-trichloroethyl chloroformate followed by zinc–acetic acid reduction. The compounds were evaluated by comparison with cocaine in causing disruption of milk intake in rats, behavioral modification in squirrel monkeys, and inhibition of ^{3}H-serotonin uptake by rat synaptosomes. The compounds showed cocaine-like activity less potent than cocaine in the latter two tests and were inactive in the milk intake test.

Keyphrases □ Cocaine analogs, various—synthesized, evaluated for effect on milk intake in rats, behavioral modifications in monkeys, and effect on ^{3}H-serotonin uptake by rat synaptosomes □ Structure–activity relationships—various cocaine analogs evaluated for effect on milk intake in rats, behavioral modifications in monkeys, and effect on ^{3}H-serotonin uptake by rat synaptosomes

Structural modifications of cocaine have been undertaken to derive compounds with the ability to interact at the cocaine receptor but with a lower intrinsic activity. Such an approach ultimately may lead to compounds with the ability to antagonize the euphoric effects of cocaine (I) as an adjunct to the treatment of cocaine abuse. Another desirable effect would be to attenuate the potent central nervous system (CNS) stimulant properties (1) of cocaine to obtain mood elevation without the prolonged latency period of tricyclic antidepressants and monoamine oxidase inhibitors. Although not defensible on any theoretical basis, previous reports on narcotic analgesics (2–6), CNS stimulants (7), and hallucinogens (8) strongly suggested the synthesis of *N*-allylnorcocaine[1] (IV), *N*-dimethylallylnorcocaine (V), and *N*-cyclopropylmethylnorcocaine (VI). This paper reports the syntheses and evaluations of IV–VI.

EXPERIMENTAL[2]

Norcocaine (III) was prepared by treatment of carbamate II with zinc and 95% acetic acid. The carbamate (II) was obtained by treating cocaine with 2,2,2-trichloroethyl chloroformate (10) and potassium carbonate in refluxing benzene. The procedure varied slightly from that described by Borne *et al.* (11) and provided similar yields. Alkylated norcocaine derivatives IV–VII were prepared by treating III with the appropriate alkyl bromide and triethylamine in refluxing benzene. Cyclopropylmethyl bromide, the only alkyl bromide not available commercially, was prepared by treating cyclopropylcarbinol with triphenylphosphine and bromine in dimethylformamide.

N-Cyclopropylmethylnorcocaine (VI) was purified by column chro-

[1] While the biological studies on these compounds were being carried out, the synthesis of *N*-allylnorcocaine and its effects on temperature, respiration, and heart rate in monkeys were reported (9).

[2] Melting points were determined on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Elemental analyses were performed by Baron Consultants, Orange, Conn. NMR spectra were obtained on a Hitachi Perkin-Elmer R-24 high-resolution NMR spectrometer using deuterated chloroform as the solvent. TLC was run on silica gel GF-254 (type 60) (EM Reagents). Column chromatography was run on silica gel 60 with a particle size of 0.063–0.200 mm (70–230 mesh ASTM) (EM Reagents). Benzene–ethanol–ammonium hydroxide (10:1:1), top phase, served as the solvent system for all chromatography.

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