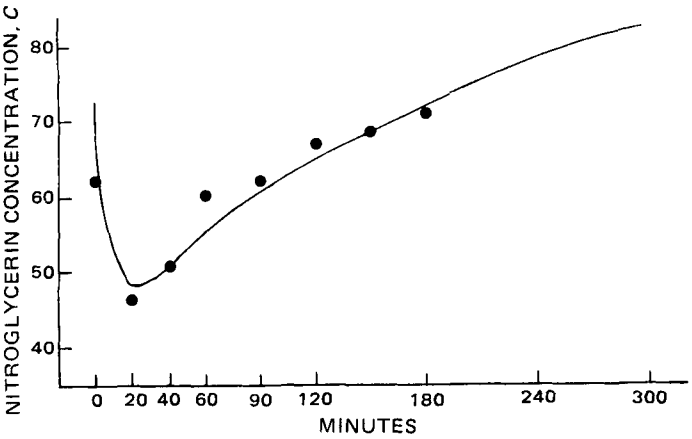

Figure 1—*Nitroglycerin loss: concentration in bottle = 100 μg/ml, flow rate = 1.0 ml/min. Equation describing loss:* $1 - (C/C_0) = 0.327e^{-0.0036t} - 0.270e^{-0.049t} + 1.08e^{-0.91t}$, *where ● is actual data and the smooth curve is computer-fitted data.*

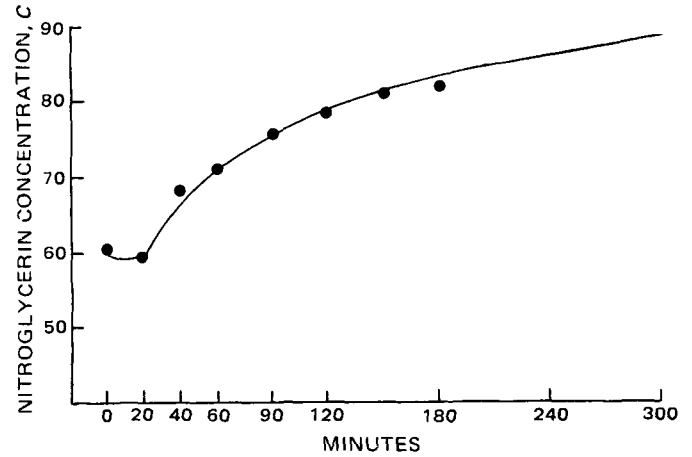

Figure 2—*Nitroglycerin loss: concentration in bottle = 100 μg/ml, flow rate = 0.5 ml/min. Equation describing loss:* $1 - (C/C_0) = 0.201e^{-0.068t} - 0.57e^{-0.004t} + 0.59e^{-0.118t}$, *where ● is actual data and smooth line is computer-fitted data.*

$$A = \frac{k_1 \frac{V_T}{V_I} C_{T_0} + k_2 C_{T_0}}{k_2 - k_{-1} - k_1 \frac{V_S}{V_I}} \qquad \text{(Eq. 10)}$$

and

$$a = k_1 \frac{V_S}{V_I} + k_{-1} \qquad \text{(Eq. 11)}$$

Finally, substituting Eq. 9 into Eq. 4 and solving for C_I:

$$C_I = \frac{k_0 C_0}{k_1 + k_3} - \left(\frac{k_0 C_0}{k_1 + k_3} - \alpha + \beta\right) e^{-(k_1 + k_3)t} + \alpha e^{-at} - \beta e^{-k_2 t} \qquad \text{(Eq. 12)}$$

where

$$\alpha = \frac{k_1 A}{a - k_1 - k_3} \qquad \text{(Eq. 13)}$$

and

$$\beta = \frac{k_1 A}{k_2 - k_1 - k_3} \qquad \text{(Eq. 14)}$$

To further simplify Eq. 12 at the initial phase, prior to adsorption of nitroglycerin, $k_1 = 0$, $k_3 = k_0$, and rearranging Eq. 12:

$$1 - \frac{C_I}{C_0} = \left(\frac{k_0}{k_1 + k_3} - \frac{\alpha + \beta}{C_0}\right) e^{-(k_1 + k_3)t} - \frac{\alpha}{C_0} e^{-at} + \frac{\beta}{C_0} e^{-k_2 t} \qquad \text{(Eq. 15)}$$

The results of the treatment of the infusion data using Eq. 15 is shown in Figs. 1 and 2, using different flow rate conditions. The data were listed using back projection (stripping) technique (2). As predicted by the model, a triexponential loss of nitroglycerin is seen. The model shows that the initial loss is due to adsorption and loss due to infusion, followed by equilibration on the inside surface of the infusion set and, consequently, the rate-limiting adsorption of nitroglycerin by the plastic. The model also shows that when no adsorption/absorption occurs, the concentration of drug delivered is the same as the concentration in the bottle.

All factors affecting nitroglycerin loss have been documented previously for static conditions (1). All these factors apply here, in addition to the loss also being dependent on the flow rate.

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Received October 13, 1981.
Accepted for publication November 27, 1981.
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General Derivation of the Equation for Time to Reach a Certain Fraction of Steady State

Keyphrases □ Pharmacokinetics—derivation of the equation for time to reach a certain fraction of steady state □ Equations—for time to reach a certain fraction of steady state, derivation

To the Editor:

The time to reach a certain fraction of a given steady-state plasma concentration for a drug which exhibits multiexponential characteristics is not a simple function of the terminal disposition rate constant or half-life. Rather, it is a complex function of all coefficients and disposition rate constants in the equation describing the concentration–time curve. A given fraction of steady state is reached sooner with a drug that demonstrates multiexponential behavior than one that demonstrates monoexponential behavior. Recently, Chiou (1, 2) developed a general equation that permits the estimation of fraction of steady state from area ratios. The derivations were based on the superposition principle, or assume constant rate input of drug into the body. The following appears to be a more general approach for the derivation of the area equation.

0022-3549/82/0400-0474$01.00/0

The plasma concentration (C) *versus* time (t) curve for a drug obeying linear kinetics can be described by:

$$C = \sum_{l=1}^{n} A_l e^{-\lambda_l t} \quad \text{(Eq. 1)}$$

following a single dose, or by:

$$C_N = \sum_{l=1}^{n} A_l \left(\frac{1 - e^{-N\lambda_l \tau}}{1 - e^{-\lambda_l \tau}}\right) e^{-\lambda_l t} \quad \text{(Eq. 2)}$$

following the administration of multiple doses at a fixed time interval of τ. In Eq. 2, C_N is the plasma concentration during a dosing interval at any time following the Nth dose. Once steady state is achieved, the concentration (C_{ss}) is given by:

$$C_{ss} = \sum_{l=1}^{n} A_l \left(\frac{1}{1 - e^{-\lambda_l \tau}}\right) e^{-\lambda_l t} \quad \text{(Eq. 3)}$$

The fraction of the steady-state concentration (f_{ss}) can be defined as the ratio of the average plasma concentration during the Nth dosing interval ($\overline{C}_N$) to the average plasma concentration at steady state ($\overline{C}$), that is:

$$f_{ss} = \overline{C}_N / \overline{C} \quad \text{(Eq. 4)}$$

where

$$\overline{C}_N = AUC_N / \tau \quad \text{(Eq. 5)}$$

and

$$\overline{C} = AUC / \tau \quad \text{(Eq. 6)}$$

AUC_N and AUC are the areas under the plasma concentration–time curves during the Nth dosing interval and at steady state, *i.e.* $\int_0^\tau C_N\,dt$ and $\int_0^\tau C_{ss}\,dt$, respectively. Integrating Eqs. 2 and 3 from time zero to τ, substituting these values for AUC_N and AUC in Eqs. 5 and 6, and solving for f_{ss} in Eq. 4 using the resulting values for $\overline{C}_N$ and $\overline{C}$ yields:

$$f_{ss} = \frac{\sum_{l=1}^{n} A_l (1 - e^{-N\lambda_l \tau})/\lambda_l}{\sum_{l=1}^{n} A_l/\lambda_l} \quad \text{(Eq. 7)}$$

This relationship for f_{ss} can be expanded to give

$$f_{ss} = \frac{\sum_{l=1}^{n} A_l/\lambda_l - \sum_{l=1}^{n} A_l e^{-N\lambda_l \tau}/\lambda_l}{\sum_{l=1}^{n} A_l/\lambda_l} \quad \text{(Eq. 8)}$$

The total area under a plasma concentration *versus* time curve following a single dose of a drug equals $\Sigma_{l=1}^{n} A_l/\lambda_l$ (*i.e.*, the integral of Eq. 1), therefore,

$$f_{ss} = \frac{AUC - \sum_{l=1}^{n} A_l e^{-N\lambda_l \tau}/\lambda_l}{AUC} \quad \text{(Eq. 9)}$$

Furthermore, the integral of Eq. 1 from time t to ∞ provides an expression for the area under a plasma concentration *versus* time curve following a single dose from time t to ∞, AUC_t^∞:

$$AUC_t^\infty \sum_{l=1}^{n} A_l e^{-\lambda_l t}/\lambda_l \quad \text{(Eq. 10)}$$

Because $N\tau$ in Eq. 9 equals the time since the beginning of dosing, *i.e.*, t, AUC_t^∞ can be substituted for $\Sigma_{l=1}^{n} A_l e^{-N\lambda_l \tau}/\lambda_l$ in Eq. 9 to yield:

$$f_{ss} = \frac{AUC - AUC_t^\infty}{AUC} = \frac{AUC_0^t}{AUC} \quad \text{(Eq. 11)}$$

Therefore, the fraction of steady state reached at time t after initiation of a multiple dosing regimen can be determined by knowing the areas, AUC and AUC_t^∞ or AUC_0^t obtained from a single dose of the drug. No model has to be assumed to permit the use of Eq. 11 for determining f_{ss}.

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Received August 13, 1981.
Accepted for publication November 23, 1981.

Hypotensive Activity of *Cecropia obtusifolia*

Keyphrases □ *Cecropia obtusifolia*—ethanol extract, hypotensive activity □ Hypotensive activity—effect of *Cecropia obtusifolia*, ethanol extract

To the Editor:

Cecropia obtusifolia Bertol is a medium-sized tree of the Moraceae family which grows wild in the tropical areas of Mexico. In the traditional medicine of tropical America, different species of *Cecropia* have been credited with a variety of therapeutic properties, such as antitussive, anti-inflammatory, and antidiarrhetic. Since the beneficial effects of extracts of *Cecropia* leaves in the treatment of heart failure were documented in a clinical study (1), it seemed of interest to determine the cardiovascular effects of *C. obtusifolia* in view of its widespread distribution in Mexico.

The material investigated[1] was collected in the area of the botanical station of Los Tuxtlas operated by the Institute of Biology of the University of Mexico and located in the Gulf coast state of Veracruz. Two kilograms of the leaves were ground and extracted with hexane in a Soxhlet apparatus. The residue was then treated with ethanol and the resulting extract dried by lyophilization. One portion of the 104-g extract was used for pharmacological studies; the other for further extraction [shown previously (2)]. The results of this work, which led to the isolation and identification of two compounds, will be reported elsewhere.

The cardiovascular activity of the extract was determined in male Wistar rats anesthetized with a 1.8 g/kg ip dose of urethane. Blood pressure and heart rate were recorded continuously, the former with a transducer connected to a cannulated femoral artery and the latter with a tachograph triggered by the pressure pulse. The extract was dissolved in propylene glycol and diluted with isotonic saline to a final concentration of 10 mg/ml, resulting in a

[1] The plant material used in this investigation was identified as *Cecropia obtusifolia* Bertol (Moraceae) by J. I. Calzada, Institute of Biology, National University of Mexico. A specimen (Number MEXU-237314) representing material collected for this investigation is available for inspection at the Herbarium of the Institute of Biology, National University of Mexico.

0022-3549/82/0400-0475$01.00/0