but the rates and magnitudes of these changes may be different. Careful attention will have to be given to the methodology of *in vitro* drug–protein binding determinations if artifactual results are to be avoided.

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The Loss of Nitroglycerin from Intravenous Administration Sets during Infusion: A Theoretical Treatment

Keyphrases □ Nitroglycerin—loss from intravenous administration sets during infusion □ Administration sets—loss of nitroglycerin during infusion

To the Editor:

In a recent report (1), a model was proposed to explain the loss of nitroglycerin from solution into a plastic bag. Under static conditions, the kinetics describing the loss of drug was biexponential and expressed as:

$$A = \beta e^{-k_3 t} + (A_0 - \beta)e^{-k_1 t} \quad \text{(Eq. 1)}$$

where A is the amount of drug in solution, k is the rate of drug absorption onto the surface of the plastic, k_3 is the diffusion of drug into the plastic, A_0 the initial amount of drug in solution, and β is a constant. With plastic bags, Eq. 1 showed an excellent fit to the experimental data.

During the infusion therapy, the above principles apply to large volume parenteral therapy. However, a dynamic situation exists in the infusion set due to the constant flow of solution through the plastic tubing. A model depicting the loss of nitroglycerin from solution when drug is diluted in a glass bottle (no absorption) and allowed to flow through the infusion set is shown in Scheme I.

In addition, because of the large amount of drug in the bottle, the tubing could become saturated. Thus, the amount of drug lost from solution is also dependent on the amount of drug present in the tubing. (It was assumed that the rate of absorption is not dependent on the amount remaining to be absorbed, $C_0 - C_T$, but on the amount present, C_T. The results appear to support this assumption.) The differential equations, therefore, describing the rate of change of C_0, C_I, C_S, and C_T are:

$$\frac{dC_T}{dt} = k_2 C_T \quad \text{(Eq. 2)}$$

$$\frac{dC_S}{dt} = k_1 C_I - k_{-1} C_S - k_2 C_T \quad \text{(Eq. 3)}$$

$$\frac{dC_I}{dt} = k_0 C_0 - k_1 C_I - k_3 C_I + k_{-1} C_S \quad \text{(Eq. 4)}$$

$$\frac{dC_0}{dt} = 0 \quad \text{(Eq. 5)}$$

To solve for this model, it must be assumed that the supply of drug in the bottle is infinite, and that the amount of drug and solution delivered through the infusion set is insignificant compared to what remains in the bottle. Solving for Eq. 2, then:

$$C_T = C_{T_0} e^{-k_2 t} \quad \text{(Eq. 6)}$$

where C_{T_0} is the saturation concentration in the tubing. To solve Eq. 3, one needs to consider the total mass balance of drug (D) in that:

$$D_0 = D_I + D_B + D_S + D_T \quad \text{(Eq. 7)}$$

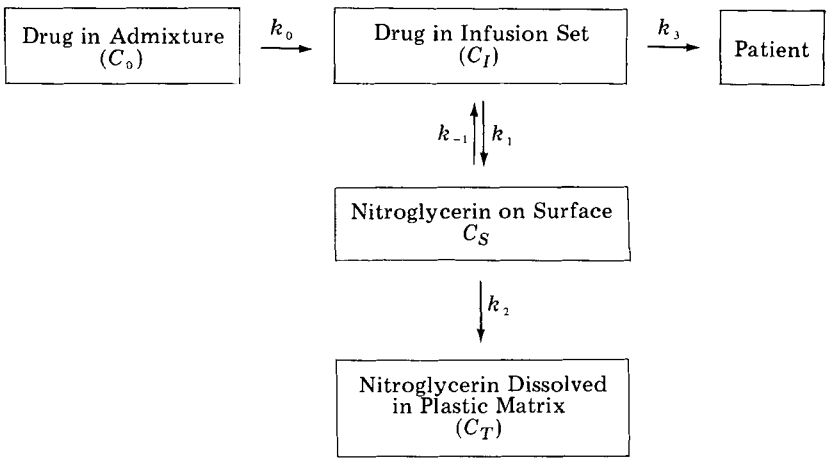
where D_0 is the total amount of drug, D_I is the drug in the infusion set (which includes the amount delivered), D_B is the drug in the bottle, D_S is the drug on the surface of the set, and D_T is the amount of drug in the plastic. Since the assumption was made that the amount of drug in the bottle is in infinite supply, then $D_0 \approx D_B$. Since D is the concentration (C) × volume (V), Eq. 7 can be approximated to be:

$$C_I = -\frac{V_S}{V_T} C_S - \frac{V_T}{V_I} C_T \quad \text{(Eq. 8)}$$

Substituting Eqs. 8 and 6 into Eq. 3, and solving for C_S, one obtains the following solution for C_S:

$$C_S = Ae^{-at} - Ae^{-k_2 t} \quad \text{(Eq. 9)}$$

where



Scheme I

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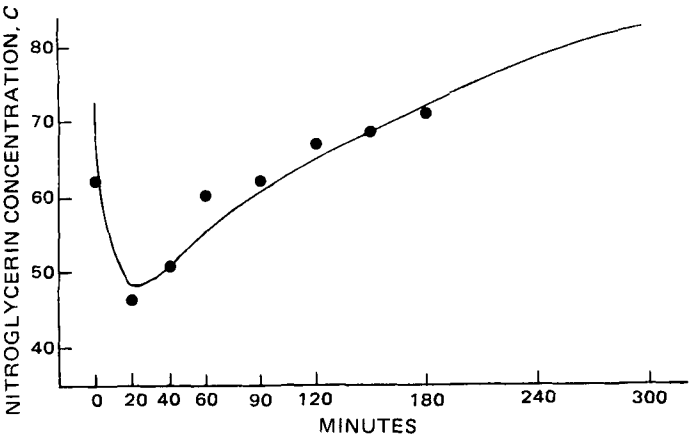

Figure 1—*Nitroglycerin loss: concentration in bottle = 100 μg/ml, flow rate = 1.0 ml/min. Equation describing loss:* $1 - (C/C_0) = 0.327e^{-0.0036t} - 0.270e^{-0.049t} + 1.08e^{-0.91t}$, *where ● is actual data and the smooth curve is computer-fitted data.*

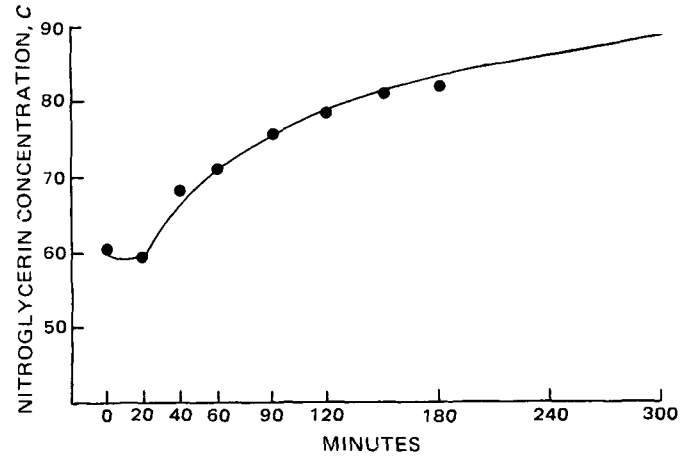

Figure 2—*Nitroglycerin loss: concentration in bottle = 100 μg/ml, flow rate = 0.5 ml/min. Equation describing loss:* $1 - (C/C_0) = 0.201e^{-0.068t} - 0.57e^{-0.004t} + 0.59e^{-0.118t}$, *where ● is actual data and smooth line is computer-fitted data.*

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

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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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.

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