Pharmacokinetic Interpretation of the Plasma Levels of Clonidine Following Transdermal Delivery

To The Editor:

The use of transdermal drug delivery to elicit a sustained systemic effect is a subject of considerable current interest. The scopolamine and nitroglycerin therapeutic systems[1-4] have recently been joined by a transdermal device containing clonidine, a potent antihypertensive agent.[5] Clonidine meets many of the criteria necessary for a drug to be delivered successfully via the skin: it is highly efficacious at low doses, it has both reasonable oil and water solubilities, and it possesses a well-balanced lipid–aqueous phase partition coefficient. The purpose of this communication is to show that, through the use of a biophysically-based model of percutaneous absorption, the physicochemical properties of the drug may be related to the design of the transdermal delivery system (i.e., its release characteristics) to predict plasma levels following topical administration of the agent. The approach is illustrated using clonidine for which pharmacokinetic data following transdermal delivery have recently been published.[5]

We have previously reported a straightforward linear pharmacokinetic model for the interpretation of in vivo percutaneous absorption data.[6] This simulation established rate constants which could be related to basic physicochemical properties of the penetrant. The initially simple approach has been extended to include specific input kinetics to the skin surface from a topical device[7] and now concentrates upon plasma concentration information rather than urinary excretion rate data. We intend to demonstrate that the successful ability of the model to simulate clonidine transdermal kinetics implies significant predictive potential. In other words, that the approach may be used prospectively both to assess potential transdermal drug candidates and to establish appropriate input rate characteristics necessary to maintain a sustained therapeutic effect.

Figure 1 illustrates the model schematically. Input kinetics from the device are described by $f(k^i)$; for a membrane-controlled patch such as that described for clonidine,[5] $f(k^i)$ consists of two parts: a first-order component (k^I) representing release from the contact adhesive[8] and a zero-order contribution (k^0) representing the membrane-controlled leaching of drug from the reservoir. The parameter k_r is included into the model for completeness. It reflects the fact that there will be competition for the drug between the patch and the skin surface. In most cases, if the system is well-designed, the partitioning will favor the skin and k_r will be negligibly small. The first-order rate constants k_1 and k_2 describe drug transport across the stratum corneum and viable epidermal tissue, respectively. Thus, k_1 and k_2 are directly proportional to the corresponding diffusion coefficients through these layers of skin and are, most simplistically, therefore, inversely dependent upon penetrant molecular weight (via the Stokes–Einstein equation[9]). The k_1 and k_2 values for benzoic acid (k_1^{BA}, k_2^{BA}) have been established by previous work[6] and may be used, with the appropriate molecular weight correction, to calculate k_1 and k_2 parameters for other penetrants (e.g., clonidine) via eqs. 1 and 2:

$$k_1 = k_1^{BA}(M^{BA}/M^C)^{1/3} \quad (1)$$

$$k_2 = k_2^{BA}(M^{BA}/M^C)^{1/3} \quad (2)$$

where M^{BA} and M^C are the molecular weights of benzoic acid and clonidine, respectively. The k_3 rate constant describes the affinity of the penetrant for the stratum corneum compared to the viable epidermis. Thus, k_3 compensates for the simplistic evaluation of k_1 and allows for greater interaction between the penetrant and the stratum corneum (thereby producing slower rates of transport out of the horny layer). The ratio k_3/k_2 may be viewed as an "effective partition coefficient" between stratum corneum and viable epidermis; the greater the ratio, the longer the penetrant transit time across the outermost skin layer. For many of the compounds analyzed with the initial kinetic approach,[6,10] k_3/k_2 appears to be linearly correlated with the octanol–water partition coefficient (K) and the relationship:

$$k_3/k_2 \simeq K/5 \quad (3)$$

describes this dependence empirically. Hence, if K is known, eqs. 1–3 can be used to estimate $k_1 - k_3$ for any penetrant on the basis of physicochemical properties alone. Finally, k_4 is the elimination rate constant of the drug from the blood. More complicated excretion behavior can be incorporated if warranted. The value of k_4 cannot be predicted but must be measured following intravenous administration of the substrate.

For the model as described (and shown in Fig. 1), it is possible to write down a series of differential equations that determine the kinetics of the transdermal absorption process. For delivery from a membrane-controlled patch, we expect both zero-order and first-order contributions to $f(k^i)$ and, on this basis, we solve the kinetic expressions for the concentration of drug in the blood (C_3) to obtain:

$$C_3 = \left\{\frac{Ak^0k_1k_2}{Vd}\left[1/\alpha\beta\varepsilon - \exp(-\alpha t)/(\alpha(\alpha-\beta)(\alpha-\varepsilon)) - \exp(-\beta t)/(\beta(\beta-\alpha)(\beta-\varepsilon)) - \exp(-\varepsilon t)/(\varepsilon(\varepsilon-\alpha)(\varepsilon-\beta))\right]\right\} + \left\{\frac{M_\infty k^I k_1 k_2}{Vd} \times \left[\exp(-\alpha t)/((\beta-\alpha)(\alpha-\omega)(\alpha-\mu)) + \exp(-\beta t)/((\alpha-\beta)(\beta-\omega)(\beta-\mu)) + \exp(-\omega t)/((\alpha-\omega)(\omega-\beta)(\omega-\mu)) + \exp(-\mu t)/((\alpha-\mu)(\mu-\beta)(\mu-\omega))\right]\right\} \quad (4)$$

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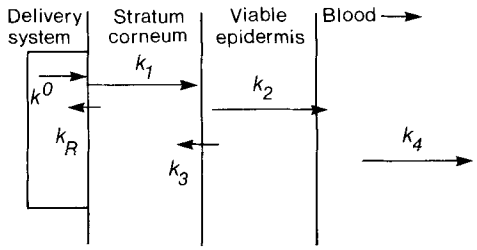

Figure 1—*Schematic representation of the transdermal delivery pharmacokinetic model.*

The first series of terms, collected in braces, is the zero-order contribution, the second is the first-order component. In eq. 4, A is the surface area of the delivery system, M_∞ is the amount of drug in the "priming" contact adhesive, Vd is the volume of distribution of the drug, and α, β, ε, ω, and μ are defined as follows:

$$(\alpha + \beta) = k_2 + k_3 + k_4;\ \alpha\beta = k_2k_4 \quad (5)$$

$$\varepsilon = k_1 + k_r \quad (6)$$

$$(\omega + \mu) = k^I + k_r + k_1;\ \omega\mu = k^Ik_1 \quad (7)$$

To predict the plasma concentration versus time profile for clonidine, we use eq. 4 with the appropriate values for the parameters required. First, as stated, we assume that k_r is small: $k_r = 1 \times 10^{-6}\ h^{-1}$. The values of k_1 and k_2 are found from eqs. 1 and 2, respectively, using known M^{BA} and M^C and published k_1^{BA} and k_2^{BA}:[6] i.e., $k_1 = 0.15\ h^{-1}$, $k_2 = 2.4\ h^{-1}$. The k_3 value is found from the octanol–water partition coefficient for clonidine ($K = 6.7$)[11] and eq. 3; thus, $k_3 = 3.2\ h^{-1}$. The volume of distribution of clonidine ($Vd = 147$ L) and the systemic elimination kinetics of the drug ($k_4 = 0.08\ h^{-1}$) have been reported.[12] For the most efficient membrane-controlled patch described recently[5] (which contains 2.5 mg of clonidine), A = 5 cm^2, $k^0 = 1.6\ \mu g/cm^2/h$, and the ratio of drug in the reservoir to drug in the adhesive is 4.3:1. Lastly, although k^I (the release kinetics of the priming clonidine dose in the patch adhesive) has not been reported, it is assumed that its value will be comparable to that exhibited by the similarly designed scopolamine therapeutic system,[1] i.e., $k^I = 1.3\ h^{-1}$.

With these parameters, eq. 4 predicts the plasma concentration–time relationship shown in Fig. 2. Both the zero-order and first-order contributions are indicated together with their summation. Also shown for comparison are the average in vivo data obtained in six normal healthy volunteers.[5] The agreement between theory and experimental observation is good. It can be seen that the "loading" adhesive dose accelerates the attainment of the steady-state plasma concentration.

Figure 2 indicates that the model over-estimates the plasma concentration at earlier times. This may reflect the suggested extensive binding of clonidine to the stratum corneum[13] or, perhaps, that the k^I value for the clonidine patch is not as large as that for the scopolamine device. If a k^I value is chosen which is closer to k_1 (e.g., $k^I = 0.1\ h^{-1}$) then an improved coincidence between theory and experiment can be achieved (Fig. 3). Additionally, it should be stated that clonidine exhibits complicated pharmacokinetics in general and that enterohepatic recycling has been documented.[14–16] The simple elimination function used in this simulation, therefore, must be considered a "first approximation" description of the systemic biodisposition. It should also be pointed out that, with a knowledge of Vd and k_4, the steady-state plasma concentration (C_3^{ss}) can be estimated from eq. 8:

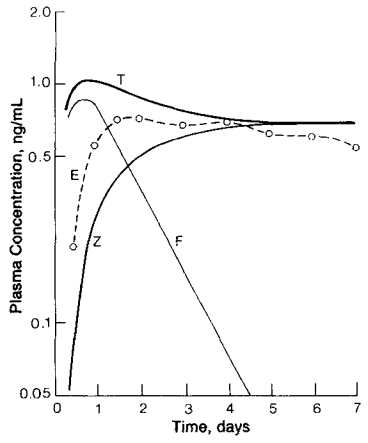

Figure 2—*Plasma levels of clonidine following transdermal delivery. Curve E shows the mean in vivo experimental data from six subjects (taken from ref. 5). Curve T is the predicted profile obtained using eq. 4. Curves F and Z are, respectively, the predicted first-order (adhesive "loading" dose) and zero-order (membrane-controlled) contributions to the complete plasma concentration–time simulation (Curve T). The kinetic constants employed for the calculations with eq. 4 were as follows (see text):* $k^0 = 1.6\ \mu g\ cm^{-2}\ h^{-1}$, $k^I = 1.3\ h^{-1}$, $k_r = 1 \times 10^{-6}\ h^{-1}$, $k_1 = 0.15\ h^{-1}$, $k_2 = 2.4\ h^{-1}$, $k_3 = 3.2\ h^{-1}$, $k_4 = 0.08\ h^{-1}$.

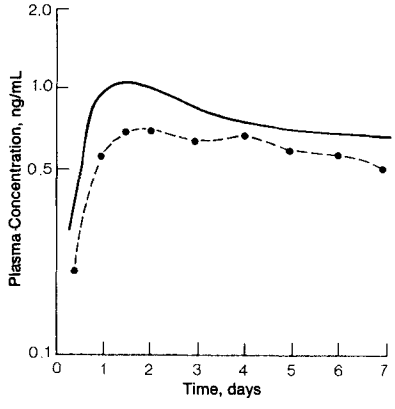

Figure 3—*Clonidine plasma levels following transdermal delivery: comparison between model prediction (——) and mean in vivo experimental data (---●---). Kinetic constants employed are the same as those given in Fig. 2 except that* $k^I = 0.1\ h^{-1}$.

$$C_3^{ss} = Ak^0/Vdk_4 \quad (8)$$

Using the values of A, k^0, Vd, and k_4 quoted above (5 cm^2, 1.6 $\mu g/cm^2/h$, 147 L, and 0.08 h^{-1}, respectively), eq. 8 predicts C_3^{ss} = 0.68 ng/mL, i.e., a value in complete agreement with the actual observations and indicative that the in vitro determined k^0 is operating in vivo.

In summary, therefore, we may conclude that the pharmacokinetic model discussed successfully predicts plasma levels of clonidine following transdermal delivery. The simulation requires known in vitro release characteristics for the device and predetermined drug elimination kinetics and volume of distribution values. However, all *transcutaneous* kinetic processes are computed directly from drug physicochemical properties alone. Research in progress suggests that similar interpretive success may be achieved for transdermal input of scopolamine and nitroglycerin.[7,17] Hence, we believe that our theoretical pathway may be useful both for screening potential transdermal delivery candidates and for the determination of optimum input kinetics in situations for which this mode of administration appears feasible.

References and Notes

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Acknowledgments

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