Pharmaceutical Research, Vol. 3, No. 6, 1986

Research Article

Engineering Targeted *In Vivo* Drug Delivery. I. The Physiological and Physicochemical Principles Governing Opportunities and Limitations

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Received April 18, 1986; accepted July 26, 1986

A physiologically based model is presented to aid prediction of the pharmacological benefits to be derived from the administration of a drug as a targeted drug–carrier combination. An improvement in the therapeutic index and an increase in the *therapeutic availability* are the primary benefits sought. A measure of the former is obtained from the value of the *drug targeting index*, a newly derived parameter. Both the drug targeting index and the therapeutic availability are directly calculable. The minimum information needed for approximating both parameters is the candidate drug's total-body clearance and some knowledge of the target site's anatomy and blood flow. Drugs with high total-body clearance values that are known to act at target tissues having effective blood flows that are small relative to the blood flow to the normal eliminating organs will benefit most from combination with an efficient, targeted carrier. Direct elimination of the drug at the target site or at the tissue where toxicity originates dramatically improves the drug targeting index value. The fraction of drug actually released from the carrier at both target and nontarget sites can radically affect index values. In some cases a 1% change in the fraction of the dose delivered to the target can result in a 50% change in the drug targeting index value. It is argued that most drugs already developed have a low potential to benefit from combination with a drug carrier. The approach allows one to distinguish clearly those drugs that can benefit from combination with targeted *in vivo* drug carriers from those drugs that cannot.

KEY WORDS: drug delivery, targeted; prodrugs; pharmacokinetics; pharmacodynamics.

INTRODUCTION

A targeted drug delivery system is one that is designated to be administered (parenterally) at a point distant from the target tissue but which finds its way preferentially to the site of action and, once there, releases the drug (1). To what extent can an *in vivo* drug carrier, such as a liposome or antibody, function as a targeted drug delivery system to improve an agent's therapeutic effectiveness through site-specific, targeted delivery? Until now there has been no systematic, theoretical approach to provide useful predictions. In this report we develop a rational basis for making such predictions.

In vivo drug delivery research aims to solve two fundamentally different problems. One is the molecular engineering task of getting known active agents to tissue and cellular sites that are normally inaccessible to that agent. The second is to improve significantly the therapeutic effectiveness of an agent that is active in its free form but lacks adequate efficacy because of unfavorable toxicity or poor pharmacokinetic properties. The first problem requires either a carrier, a prodrug, or a combination of the two that is capable of overcoming an *in vivo* barrier. Stella and Himmelstein (2,3) provide an excellent discussion of favorable and unfavorable situations for molecular modifications or prodrugs overcoming such barriers and improving site-specific drug delivery. Potential solutions to the second problem that are based on utilization of drug carriers and include consideration of toxicity have not received such detailed theoretical study. In many instances the use of a drug–carrier combination and molecular modification to produce a prodrug are simply different means to the same end.

The thesis presented here builds on that presented by Stella and Himmelstein (2,3) and is that the physicochemical properties of an agent—a traditional drug, a peptide, or a protein—and the properties of both the target and the nontarget sites are critical in predicting when a targeted carrier can either improve the therapeutic efficacy or increase the apparent potency. We begin by assuming that targeted carriers can be engineered with built-in rate control[3] and that they will be capable of delivering up to 100% of an agent to

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[3] An *in vivo* drug carrier must accomplish two things: it must get the therapeutic agent to the target tissue and then release the agent at a reproducible rate. The design of the carrier should allow one some degree of control over the release rate profile.

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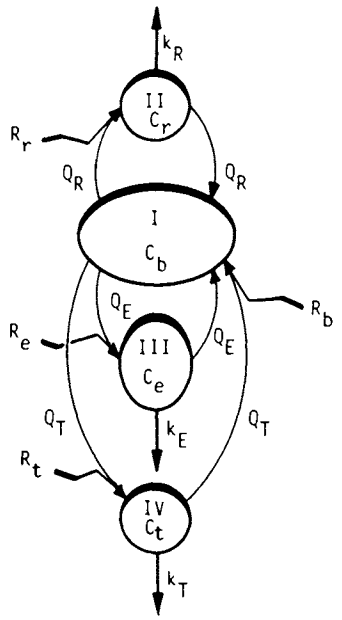
any given set of target sites. We then employ a pharmacokinetic model to generate equations for calculating two new parameters: *therapeutic availability* and *drug targeting index*. These parameters allow predictions of the magnitude of the improved therapeutic efficacy or increased apparent potency that would result when the drug is administered as a drug–carrier combination. They allow one to identify specific physicochemical, pharmacokinetic, and physiological attributes that a drug and its corresponding target must meet for either to be a rational candidate for targeted drug delivery.

THEORETICAL

The Model

When one is interested in the potential benefits of administering a drug as a drug–carrier combination, some information on the drug's site of action will usually be available along with some information on the drug's pharmacokinetic properties. We assume that the species of interest is man. We prefer a model that can directly utilize available information to, at least, make predictions about the order of magnitude of any potential benefit.

A general and adequate model for this discussion is Scheme I. It describes the pharmacokinetic properties of a range of real and hypothetical drugs.[4] Compartment II represents all tissues containing target sites for the desired response and has an effective blood-flow rate of Q_R. It is subsequently referred to as the response compartment. The effective drug concentration at these target sites that is available to initiate the pharmacological cascade is designated C_R when the drug is administered in its free form and C_r when the drug dose is administered as a drug–carrier combination. To facilitate building a theoretical foundation, we assume that the effective concentration at the action site is a function of the measurable concentration in that tissue's exiting venous blood or plasma (whichever is the reference fluid), as discussed in the Appendix. Situations where partitioning between the response sites and blood is rate limiting or where there is poor partitioning between blood and response sites are briefly addressed both in a later section and in the Appendix.



Scheme I

Compartment IV, the toxicity compartment, represents tissues containing nontarget sites where the cascade of events leading to a toxic response is initiated and has an effective blood flow Q_T. The effective concentration of drug at these sites is designated C_T when the drug is administered in its free form and C_t when the drug is administered as the same drug–carrier combination. It is understood that if these nontarget sites are located in the same tissue as target sites, then a drug carrier is unlikely to provide the desired improvement in therapeutic efficacy.

Compartment III is designated the elimination compartment. It represents both liver and kidney and has a blood flow Q_E. Drug elimination is controlled by k_E. Additional elimination processes associated with the response and toxicity compartments are shown. They combine elimination and metabolism. All metabolites are assumed to be inactive. Compartment I represents blood and all other tissues not accounted for by the other three compartments. Blood flow within this compartment is limited to total cardiac output minus $(Q_R + Q_T + Q_E)$. To distinguish compartment I from the traditional pharmacokinetic central compartment, it is subsequently referred to as the blood compartment. The blood level of drug in this compartment is designated either C_B or C_b when free drug or a drug–carrier combination, respectively, is administered.

Drug delivery is designated by one of two different input functions for each of the four compartments: R_B is the intravenous input function for free drug; R_b, R_r, R_e, and R_t are the release rates (and also input functions) of free drug from the carrier, as illustrated in Scheme I, into each of the corresponding compartments when the drug is actually administered as a drug–carrier combination. When $R_b = R_t = R_e = 0$, the drug carrier is an ideal target-specific drug carrier. We assume that as long as drug remains associated with the carrier, regardless of its location *in vivo*, it is inactive. Note that neither the blood nor the tissue level of the drug–carrier combination is referred to in Scheme I or in any of the subsequent equations.

Operational Equations

Changing the effective physicochemical properties of drugs with the use of liposomal or macromolecular drug carriers is expected to provide either an improved therapeutic index or an apparent increase in potency (7–9). Once drug has been released from the carrier, however, the influence of the carrier is assumed to be lost and the drug is expected to have the same local pharmacokinetic properties as when it is administered in free form (10). We assume that the carrier

[4] Scheme I is a simplified version of the anatomic, tissue perfusion models first presented by Bellman *et al.* (4) and later simplified by Bischoff (5) to allow useful pharmacokinetic simulations. Scheme I is also a simplified version of a flow model used by Øie and Huang (6) to quantify the advantage of direct arterial administration of a drug to a specific tissue.

has no significant pharmacological or toxic properties of its own. The intravenous route is a convenient reference administration route for either free drug or the drug–carrier combination, and so we restrict attention to this route.

Equations (1)–(4) are the set of differential equations that describes the model in Scheme I when free drug is given intravenously, consistent with the definitions and limitations given above.

$$V_B\frac{dC_B}{dt} = -(Q_R + Q_E + Q_T)C_B + Q_RC_R + Q_EC_E + Q_TC_T + R_B \quad (1)$$

$$V_R\frac{dC_R}{dt} = Q_RC_B - Q_RC_R - k_RV_RC_R \quad (2)$$

$$V_E\frac{dC_E}{dt} = Q_EC_B - Q_EC_E - k_EV_EC_E \quad (3)$$

$$V_T\frac{dC_T}{dt} = Q_TC_B - Q_TC_T - k_TV_TC_T \quad (4)$$

The constants V_B, V_R, and V_T are the apparent volumes of distribution of the corresponding compartments. The constants k_R, k_E, and k_T are the apparent, first-order elimination rate constants. The term R_B is the rate of intravenous drug input, and $\int_0^\infty R_B dt = D$, where D is the dose. When drug is administered intravenously as the drug–carrier combination, the alternate set of differential equations is given by Eqs. (5)–(8).

$$V_B\frac{dC_b}{dt} = -(Q_R + Q_E + Q_T)C_b + Q_RC_r + Q_EC_e + Q_TC_t + R_b \quad (5)$$

$$V_R\frac{dC_r}{dt} = Q_RC_b - Q_RC_r - k_RV_RC_r + R_r \quad (6)$$

$$V_E\frac{dC_e}{dt} = Q_EC_b - Q_EC_e - k_EV_EC_e + R_e \quad (7)$$

$$V_T\frac{dC_t}{dt} = Q_TC_b - Q_TC_t - k_TV_TC_t + R_t \quad (8)$$

This set of equations includes four drug input functions, R_r, R_t, R_e, and R_b, such that $\Sigma\int_0^\infty(R_i)dt = D'$, where D' is the total amount of drug released from the drug carrier. For convenience, we set $D' = D$. A reasonable assumption is that the various mechanisms governing drug release will be similar at the response and other tissue sites. Under these conditions the rates of drug release can be combined and rewritten as

$$R_b + R_r + R_e + R_t = (F_b + F_r + F_e + F_t)R_o = R_B \quad (9)$$

where R_o is the average *in vivo* drug release rate from the total carrier dose, and the F_i terms are the fractions of drug release occurring in each of the four compartments, so that $R_t = F_tR_o$, etc. One or more F_i values can equal zero. Further, to compare the relative benefit derived from the drug–carrier combination to that resulting from intravenous administration of free drug, we set $R_B = R_o$.

The most frequently reported pharmacokinetic property of a drug is its total-body clearance. Often, information is also available on the drug's extraction ratio from blood by the clearing organs. It is more convenient to express elimination from the three compartments in terms of known blood flows and estimable tissue extraction ratios. The extraction ratio, E, for a drug by an organ or tissue is traditionally defined by

$$E = \frac{C_{in} - C_{out}}{C_{in}} \quad (10)$$

where C_{in} is the arterial blood concentration and C_{out} is the venous blood level. The rate of elimination from the i^{th} compartment in Scheme I is given by $k_iV_iC_i = (C_B - C_i)Q_i = Cl_iC_B$, where Cl_i is the blood clearance from the ith compartment. Using $E_i = (C_B - C_i)/C_B$, and solving for k_iV_i at steady state gives

$$k_iV_i = \frac{Q_iE_i}{(1 - E_i)} \quad (11)$$

For Scheme I, i = R, E, or T. Total clearance is $(Q_EE_E + Q_RE_R + Q_TE_T) = (Cl_E + Cl_R + Cl_T) = Cl_{tot}$. Finally, we define the relative blood-flow parameters n and m by the relations

$$Q_E = nQ_R \quad \text{and} \quad Q_T = mQ_R \quad (12)$$

For the vast majority of drugs both the response and the toxicity are a function of the time course of drug at the target and toxicity sites, respectively. Single measurement descriptions of the critical pharmacokinetic property at these sites include the area under the site–concentration time curve, the steady state drug level, the peak drug level, and the duration above some minimum effective level. We limit attention to drugs where either the area measurements or the steady-state levels provide sufficient information for reasonably estimating the drug effect and toxicity. The expected ratio of drug delivered to response and toxicity sites when the drug–carrier combination is used, divided by the same ratio when free drug is administered intravenously, is the best measure of the effectiveness of the carrier. We call this ratio of ratios the *drug targeting index*, **DTI**.

Let AUC_i designate the area under the drug level vs time curve in the i^{th} compartment. The drug targeting index can therefore be defined as

$$DTI = \frac{AUC_r/AUC_t}{AUC_R/AUC_T} = \left[\frac{C_r/C_t}{C_R/C_T}\right]_{ss} \quad (13)$$

where the ss subscript designates steady state. Lowercase subscripts identify values when the drug–carrier is used; capital subscripts identify values when free drug is used. When Eqs. (1)–(8) are solved for each of the dependent variables in Eq. (13) (see Appendix), it is seen that the numerical value of DTI for each of the ratios in Eq. (13) is the same:

$$DTI = \frac{F_b + (1 + nE_E + mE_T)F_r + (1 - E_E)F_e + (1 - E_T)F_t}{F_b + (1 - E_R)F_r + (1 - E_E)F_e + \left[\frac{E_R}{m} + \frac{nE_E}{m} + 1\right]F_t} \quad (14)$$

If the carrier is ideal, i.e., $F_b = F_e = F_t = 0$, then Eq. (14) reduces to

$$DTI = \frac{1 + nE_E + mE_T}{1 - E_R} \quad (15)$$

Only a minority of drugs is actually eliminated at either response or toxicity sites. If $nE_E \gg mE_T$ and $E_R \ll 1$, then Eq. (15) reduces to[5]

$$DTI = 1 + nE_E = 1 + \frac{Q_E E_E}{Q_R} \quad (16)$$

Therapeutic Index

The therapeutic index, TI (also therapeutic ratio), is a statistical measurement defined as the ratio of the median toxic dose to the median effective dose (13). There is a maximum tolerated toxic dose (MTTD) and a minimum effective dose (MED) for each individual. For convenience, the median toxic dose is defined as the mean of the individually determined maximum tolerated toxic doses. The median effective dose is defined as the mean of the individually determined minimum effective doses. Therefore, the therapeutic index is identical to the ratio of the typical individual's MTTD and MED values:

$$TI = MTTD/MED \quad (17)$$

There are many ways to quantify both clinical response and toxicity. Temporal measurements that allow quantitation of the duration of effect, the magnitude of the effect, and its occurrence relative to dosing are preferred, and so we define the total response (or toxicity) as the area under the response (or toxicity) vs time curve. In order to relate more easily the therapeutic index to Scheme I, attention is restricted to drugs that meet two additional conditions. When the drug is administered as a targeted drug–carrier combination, a new dose, the carrier-derived minimum effective dose (MED′), is expected to generate the same response as is produced by the free-drug MED. Also, another dose, the carrier-derived maximum tolerated toxic dose (MTTD′), is expected to be required to generate the same toxicity as is produced by the MTTD. The therapeutic index for the drug–carrier combination, TI′, thus becomes the ratio of these new carrier-derived values:

$$TI' = MTTD'/MED' \quad (18)$$

The relationships between the above two measures of therapeutic index, the minimum effective dose, etc., are illustrated in Fig. 1 for a hypothetical drug in a typical individual.

It can readily be seen (Appendix) that for the conditions specified, the ratio of TI′ to TI will be a constant that is identical to the drug targeting index defined in Eq. (14):

$$DTI = TI'/TI \quad (19)$$

Equation (19) states that for the typical individual the ratio of the therapeutic index value obtained from a drug–carrier combination to that obtained from an equal dose of the free drug will be a constant that is independent of the total dose (or dose rate) for a specified drug carrier but uniquely dependent on the fraction of the dose delivered by the carrier to the various tissues.

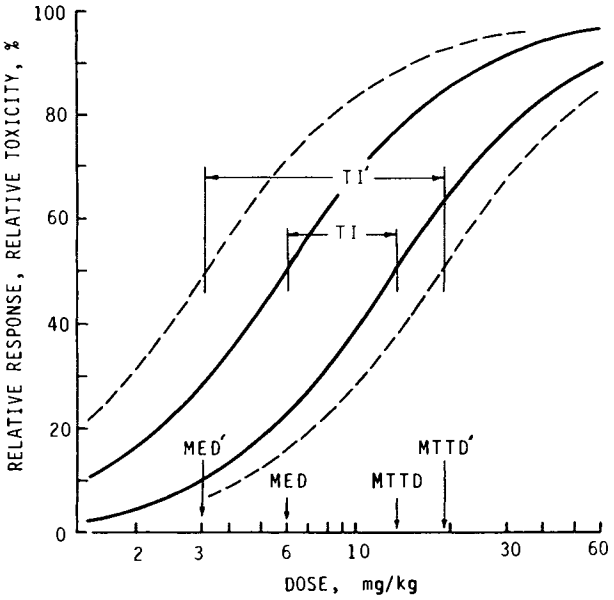


Fig. 1. The therapeutic index is illustrated by a plot of both relative response (two left curves) and relative toxicity (two right curves) vs dose for a hypothetical drug in a person typical of the population median. The two dashed curves illustrate an example of the expected change in relative response and toxicity (solid curves) when the drug is administered as a drug–carrier combination that gives a new, larger therapeutic index, TI′. MED, minimum effective dose for free drug; MTTD, maximum tolerated toxic dose for free drug; MED′ and MTTD′, the corresponding values when the drug–carrier combination is administered. For this example TI = 1.9, TI′ = 5.6, and DTI = 2.9. Relative response is given by $P/P_{max} = D^n/(\kappa' + D^n)$; relative toxicity is given by $T/T_{max} = D^n/(\kappa + D^n)$, where κ', κ, and n are arbitrarily selected constants, and D is the dose in mg/kg. The values were $\kappa' = 14.5$, $\kappa = 50$, and $n = 1.5$, respectively; for the drug–carrier case they were $\kappa' = 6$, $\kappa = 80$, and $n = 1.5$, respectively.

Therapeutic Availability

If the therapeutic index for the free drug is large, then improving it further by using an *in vivo* drug carrier is unlikely to yield a significant clinical advantage. It could, however, considerably reduce the actual dose needed to get the desired effect. To quantify this property we define a new term: *therapeutic availability*, TA. Analogous to the definition of the drug targeting index, the therapeutic availability can be defined as a ratio of either AUC values or steady-state levels. In both cases the result (Appendix) is the same:

$$TA = \frac{AUC_r}{AUC_R} = \left[\frac{C_r}{C_R}\right]_{ss} \quad (20)$$

[5] Equation (16) is similar to one published by Chen and Gross (11) to describe the advantage (in terms of amount of drug) of intraarterial drug delivery (R_d) to a tumor: $R_d = 1 + (K_{app}/Q_T)$, where K_{app} is the total apparent drug clearance from the body and Q_T is the blood-flow rate in the tumor region. Øie and Huang (6) develop this concept further using a physiologically realistic multicompartment model. Equation (16) is also similar to an expression presented in a preliminary report on this topic (12) and was based on a simple open, two-compartment pharmacokinetic model.

The therapeutic availability is the ratio of the dose fraction reaching target sites when the dose is administered parenterally as a drug–carrier combination to the amount reaching the same sites when an equal dose of the free drug is administered intravenously. It is useful to note that the therapeutic availability is also the ratio of the mean residence time (14) for the drug in the response compartment when it is administered as the drug–carrier combination to the mean residence time for the drug in the same compartment when it is administered as free drug. Clearly, if the carrier produces an increase in the drug's response-compartment mean residence time, then the apparent potency will increase.

The value of therapeutic availability can be calculated from either ratio in Eq. (20) when there are equal doses. Incorporation of the appropriate values of the dependent variables in Eq. (20) (Appendix) leads to a definitive expression for therapeutic availability:

$$TA = F_b + (1 + nE_E + mE_T)F_r + (1 - E_E)F_e + (1 - E_T)F_t \quad (21)$$

The maximum possible increase in therapeutic availability occurs when $F_b = F_e = F_t = 0$ and is

$$TA = 1 + nE_E + mE_T \quad (22)$$

When $nE_E \gg mE_T$ and $mE_T \ll 1$, the maximum value of therapeutic availability is identical to the drug targeting index value given by Eq. (16).

RESULTS

Simplifications and Restrictions for Currently Used Drugs

Equation (14) has eight variables, too many even for a modest evaluation of the drug targeting index as each variable is changed independently. Therefore, several variables are limited. Total blood flow is limited to cardiac output: 5 liters/min, in a normal 70-kg human. Values of Q_R are arbitrarily limited to between 1 and 20% of the cardiac output. Blood flow to the eliminating organs, Q_E, is often fixed at 54% of the cardiac output (i.e., 2.7 liters/min in man: 1.5 liters/min for liver plus 1.2 liters/min for kidney), which in turn limits the range for n values. The value of m is limited to 0.33, 1.0, or 3.0. We focus on drugs that have either high, medium, or low total clearance values. The mean group value is arbitrarily set at 75, 50, or 25% of the combined liver and kidney blood flow, i.e., 40.5, 27, or 13.5% of the cardiac output, respectively.

Clearance values are available for 178 drugs currently used in man (15). These values yield useful statistics[6] that add perspective to this discussion. The range representing approximately 68% of the tabulated drugs is 81–1873 ml/min for a 70-kg person or 1.6–37.5% of the cardiac output; the average drug's clearance is 389 ml/min[6] or 7.8% of the cardiac output. Assuming that the tabulated values are representative of all currently used drugs, then 14% of them have total clearance values greater than 40.5% of the cardiac output (our value for a high-clearance drug), 79.4% of current drugs have clearance values less than 27% of the cardiac output, and 63.7% have clearance values less than 13.5% of the cardiac output (our low clearance value). Our simulations focus on the higher-clearance drugs.

Changes in Therapeutic Availability at Constant Total Clearance

Therapeutic availability, unlike the classical term bioavailability, can have values either greater than or less than one. An increase in therapeutic availability is effectively equivalent to an increase in potency. If, for example, a drug–carrier combination has a therapeutic availability value of 6.0, then one-sixth of the dose D_i, when administered as the drug–carrier combination, will have the same effect as giving that dose intravenously as free drug.

Figure 2 shows therapeutic availability as a function of Q_R when the total clearance of hypothetical drugs was held constant at either a high, a medium, or a low clearance value. Results are shown when $E_R = 0$ (solid curves) and when $E_R = 0.5$ (dashed curves). The value of m is fixed such that $Q_T = Q_R$. Note that changes in n (Q_E/Q_R) must be counterbalanced by changes in E_E if clearance is to be kept con-

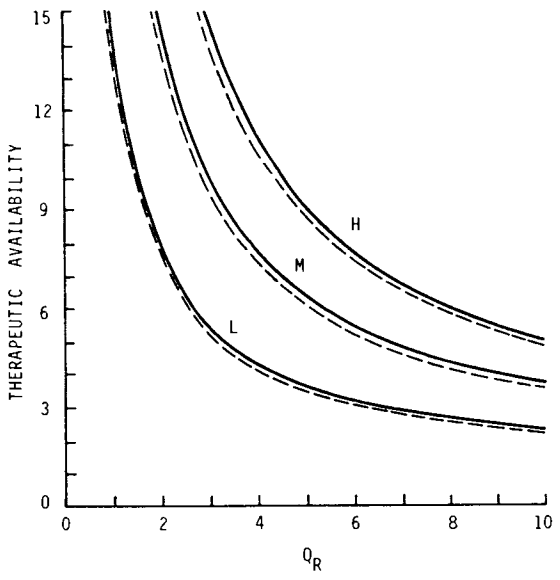


Fig. 2. The therapeutic availability is plotted against the effective blood flow to the response site (target compartment), Q_R, expressed as a percentage of the cardiac output, for a range of hypothetical drugs having either a high (H), a medium (M), or a low (L) total clearance value. Therapeutic availability was calculated from Eq. (22). Solid curves were generated by designating $m = 1$, $E_R = 0$. Dashed curves were generated by setting $E_R = 0.5$. High, medium, and low clearance values are defined as 40.5, 27, and 13.5% of the cardiac output, respectively, which in turn are 75, 50, and 25% of Q_E, respectively.

[6] The values in Ref. 15 are plasma clearance values and are reported as ml/kg-min. When one assumes that the values are log-normally distributed, one obtains the following results ($n = 176$): mean of $\ln X = \bar{Y} = 0.9704$; s (for $\bar{Y}$) = 1.572 (two extremely high clearance values were treated as outliers and were not included in the calculation). Thus, $\bar{X} = 2.639$ ml/kg-min. Multiplying $\bar{X}$ by 70 kg and dividing by 0.475, a typical hematocrit value, converts this clearance value to a total blood clearance for a 70-kg human of 389 ml/min. This conversion assumes that the partition coefficient between plasma and red cells is 1. The corresponding range for $e^{\bar{Y}} \pm e^{s}$—representing approximately 68% of the drugs tabulated—is 81–1873 ml/min.

stant. Each curve is generated for $F_r = 1$, an ideal carrier. We see that, regardless of a drug's total clearance, substantial increases in therapeutic availability can be produced when the target sites have blood flows that are a small percentage of the cardiac output.

If one conservatively selects a minimum acceptable value of 10 for therapeutic availability, then it is clear from Fig. 2 that a perfect carrier ($F_r = 1$) can deliver this value when the drug's total clearance is high and the value of Q_R is less than 5% of the cardiac output. If the total clearance is lower, then Q_R must also be lower for therapeutic availability to reach or exceed a value of 10.

Drug Targeting Index for Ideal Carriers

When the carrier is ideal, Eq. (15) rearranges to

$$\text{DTI} - 1 = \frac{\text{total clearance}}{Q_R(1 - E_R)} \tag{23}$$

Values of DTI − 1 are graphed in Fig. 3 as a function of E_R. It is clear that large DTI values are possible only under specific conditions. The maximum value of DTI is directly proportional to the total clearance and can be dramatically influenced by E_R. Smaller values of Q_R allow larger maximum DTI values. Figure 3 shows that a low-clearance drug will have a maximum DTI value of 2.35 when Q_R = 10% of the cardiac output and there is no significant elimination of drug at the response site, whereas another compound acting at the same target and having the same total clearance will have a maximum DTI value of 9.0 if it has a 0.85 response-site extraction ratio.

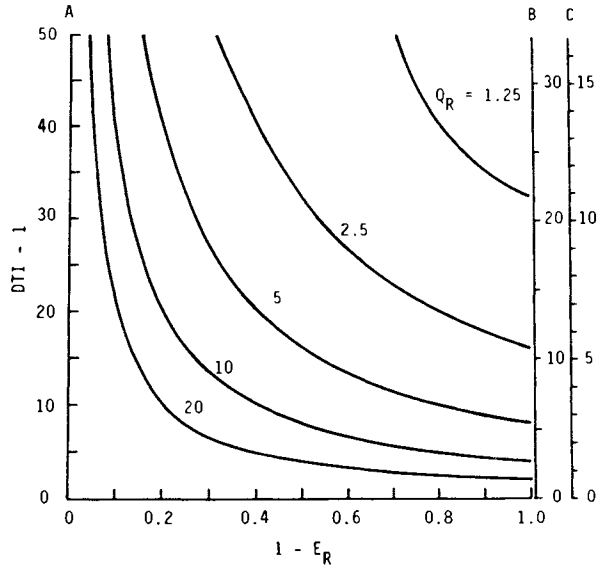


Fig. 3. The dependence of the drug targeting index [Eq. (23)] on the extraction ratio of the response compartment (E_R) is shown. Each curve is for a fixed value of Q_R ranging from 20 to 1.25% of the cardiac output. Ordinate A designates DTI values for the set of drugs having a high total clearance value, ordinate B is for the set having a medium total clearance, and ordinate C is for the set having a low total clearance.

The Drug Targeting Index When the Carrier Is Less Than Perfect

In practice no carrier is likely to provide completely efficient targeting. Figure 4 illustrates the expected decline in the maximum drug targeting index value as the release of drug from the carrier is shifted away from target sites to other tissues. Examples are arbitrarily limited to cases where $E_R = E_T = 0.05$. In each case the values of m are 0.333, 1.0, and 3.0. Suboptimum targeting was simulated by setting $(1 - F_r)$ equal to either F_e, F_b, or F_t.

Figure 4A is for a high-clearance drug; target and toxicity sites are characterized by Q_R = 1.25% of the cardiac output. The decline in DTI is not directly proportional to the decline in F_r. As expected, DTI declines most dramatically when $(1 - F_r) = F_t$. Reducing F_r from 1.0 to 0.95—a 5% decline—reduces DTI from 66 to 6.0—a 91% decline. Having some drug carrier intercepted by the elimination compartment, i.e., $1 - F_r = F_e$, gives a much less dramatic drop in DTI: a 25% decline in F_r—from 1.0 to 0.75—reduces DTI by only 13% percent; whereas if that same 25% decline in drug release is shifted to blood, then DTI would be reduced by 36%. Increasing m from 0.333 to 3.0 shifts 4% of the total clearance from the elimination compartment to the toxicity compartment. This shift does not significantly alter DTI when $1 - F_r = F_b$; it slightly reduces DTI when $1 - F_r = F_e$. However, it dramatically *increases* DTI when $1 - F_r = F_t$.

Another interesting prediction is illustrated by the dotted curves in Fig. 4A: E_E was increased to 0.95 in case a and to 0.98 in case b. For the extreme conditions where targeting is inefficient, i.e., $F_r < 0.025$, a 1% increase in the fraction of the dose delivered to the target can result in a 50% increase in the value of DTI.

The simulations in Figs. 4B and C illustrate the reduction in DTI values as the total clearance declines from a medium to a low value. When clearance is maintained at a high value (Figs. 4D–F), and Q_R and Q_T/m are increased to 2.5, 5, and finally 10% of the cardiac output, the pattern for the declining DTI values as $F_r \to 0$ is similar, although the magnitude of DTI declines in proportion to the increase in Q_R when $(1 - F_r) = F_b$ or F_e. Interestingly, however, when $(1 - F_r) = F_t$, the actual value of DTI is approximately the same for each Q_R at fixed values of $F_t \geq 0.05$.

Minimum Requirements

Figure 5 shows the ideal case when $F_r = 1$. It shows the required values for variables in Eq. (23) such that DTI = 5 or 10. Total clearance is fixed at the previous high, medium, or low values. Consider the example of a medium clearance drug with no target-site elimination ($E_R = 0$). If the minimum acceptable value of DTI is 10, then the drug's target site must have a blood flow that is ≤3% of the cardiac output to meet the qualification. However, for another medium-clearance drug characterized by $E_R = 0.4$, the target site need only have a blood flow of ≤4.5% of the cardiac output to qualify. Consider another example where the target site is known to have a blood flow of 7% of the cardiac output. No medium- or low-clearance drug with $E_R \leq 0.4$ can meet the qualification. A high-clearance drug can meet the qualification only if $E_R \leq 0.38$, and such high target extraction ratios

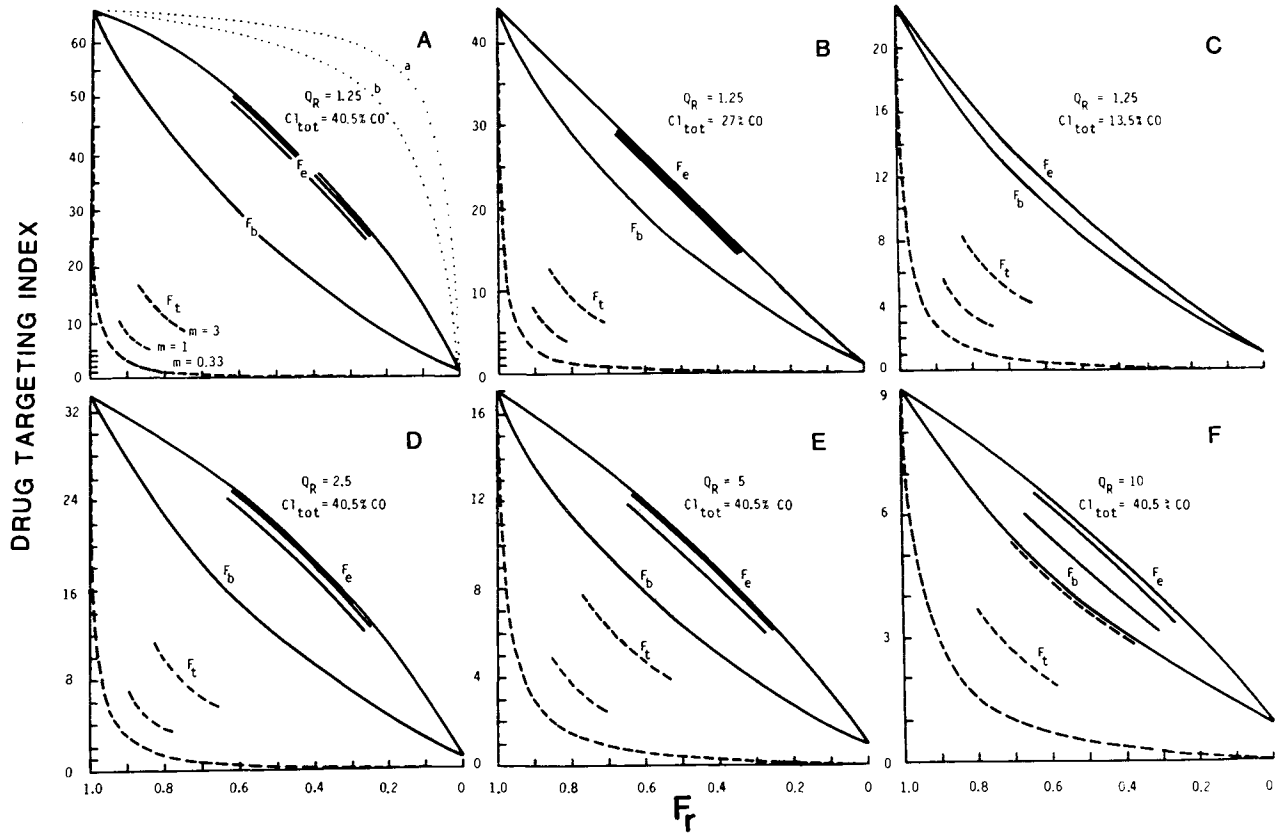


Fig. 4. The dependency of the drug targeting index on the fraction of the dose actually delivered to the target site (F_r) is shown. For curves labeled F_b, that drug not delivered to the response site is delivered to blood: $(1 - F_r) = F_b$ and $F_e = F_t = 0$. For curves labeled F_e, $(1 - F_r) = F_e$, and for curves labeled F_t, $(1 - F_r) = F_t$ (dashed curves). For each of these conditions $m = 0.333$ (complete curves), 1.00 (partial curve), or 3.0 (partial curve) and $E_R = E_T = 0.5$. The value of Q_R, as a percentage of the cardiac output (CO), is designated in each case. In each panel the total clearance is constant. (A) For the solid curves $n = 43.2$ and E_E ranges from 0.735 ($m = 0.333$) to 0.615 ($m = 3.0$); for the dotted curve labeled a, $n = 31.7$, $m = 0.333$, and $E_E = 0.98$; for the dotted curve labeled b, $n = 32.7$, $m = 0.333$, and $E_E = 0.95$. (B) E_E ranges from 0.485 ($m = 0.333$) to 0.454 ($m = 3.0$). (C) E_E ranges from 0.235 to 0.204. (D) E_E ranges from 0.627 to 0.380. (E) E_E ranges from 0.679 to 0.556. (F) E_E ranges from 0.627 to 0.380.

are rare. However, if $E_R \simeq 0$, then only a drug having a total clearance substantially greater than 40.5% of the cardiac output (75% of Q_E) can qualify.

DISCUSSION

No drug carrier has come close to functioning ideally in experimental model systems. Equations (14) and (21) can, therefore, be quite useful for deciding if a particular drug is a reasonable drug-carrier candidate. They are equally useful in determining when the physiology characterizing a specific therapeutic situation can be exploited by a drug–carrier combination. It is clear from Eq. (15) that drugs with high total clearance values are more likely to be good candidates and that response sites with effective blood-flow rates that are a small fraction of the blood flow to the eliminating organs ($n = Q_E/Q_R$) are the best candidates for combination with an appropriately designed drug carrier.

Limitations of the Model

The major limitation of Eqs. (14) and (21) is the collection of simplifications and limitations that allowed their derivation. Some of these restrictions are necessary, but several can be relaxed. The concentration of drug at the action site can be different from the tissue's exiting venous concentration.[7] In some of these cases Eqs. (14) and (21) remain valid (Appendix). Equations (1)–(8) do not cover situations where access to or egress from an action site remains the intracompartmental rate-limiting step despite R_i (16). Even so, as argued in the Appendix, Eqs. (14) and (21) will be valid in many circumstances. The stipulation of dose-independent pharmacokinetics does narrow the scope of application of the drug targeting index but is essential for maintaining simplicity at this stage of development. The possibility of differences in the character of either the response or the toxicity resulting from doses of free drug and a drug–carrier combination is not ruled out but is not dealt with here. Examples that are not covered include situations where the effect (or toxicity) is proportional to either the total cumulative drug exposure or the total area under that portion of the site's drug level vs time curve above some specified level. Such

[7] The blood or elimination compartments in Scheme I may have slowly equilibrating regions. However, they do not complicate the quantitation of the model with respect to response or toxicity as given by Eq. (14).

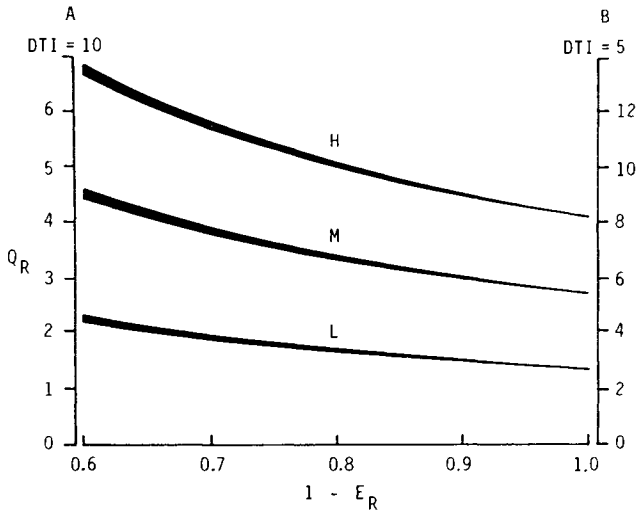
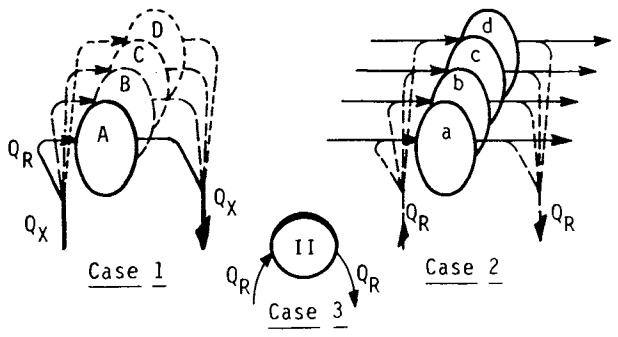


Fig. 5. The values of Q_R that are required for an ideal, targeted carrier (F_r = 1) to generate a DTI value of either 10 (ordinate A) or 5 (ordinate B) are plotted vs (1 − E_R) for hypothetical drugs having either high (H), medium (M), or low (L) total clearance values. Any point above a specific curve results from combinations of Q_R and (1 − E_R) that generate DTI values less than either 10 (ordinate A) or 5 (ordinate B); any point below a specific curve results from DTI values more than either 10 or 5.

limitations become less significant when one is interested primarily in order-of-magnitude estimates of the drug targeting index or therapeutic availability.

Situations where either response sites or toxic sites are evenly dispersed throughout a single tissue or organ, as depicted in Scheme I, are not in the majority. One also encounters situations where target sites are associated with cellular subsets of a single tissue or organ. At the other extreme one can encounter situations where action sites are dispersed through two or more anatomically distinct tissues. Equations (14) and (21) can cover some of these variations. Case 1 in Scheme II depicts a single tissue composed of four cellular subsets, A–D, with a blood flow of Q_x, and subset A containing the action sites. Assume that the fraction of tissue accounted for by A (based possibly on either volume fraction, weight fraction, or protein fraction) is $f = Q_R/Q_x$. The tissue subsets in Case 1 can therefore be conceptually segregated into two or more compartments, as illustrated, with the target sites getting an *effective* blood flow of Q_R = fQ_x. The tissue subset A can thus be converted into Case 3, which in turn represents the response compartment in Scheme I. The remainder of the tissue, with a flow $(1 - f)Q_x$, would then be combined with other tissues comprising one of the other three compartments. Case 2 depicts a situation where four anatomically distinct tissues, with separate but known blood flows, each contain target sites. These tissues may be conceptually combined, as illustrated, such that their blood flows sum to Q_R, and subsequently treated as Case 3. Of course, similar arguments can be applied to toxic sites and the definition of toxicity compartment.



Scheme II

Therapeutic Availability

The therapeutic availability quantifies the increase in the amount of drug reaching target sites when administered as a drug–carrier combination compared to when the same dose is administered intravenously. If the primary value of a drug carrier is to reduce the dose, as opposed to increasing the therapeutic index, then the preferred value of therapeutic availability is expected to be much larger than a corresponding preferred value of the drug targeting index. The advantage of a lower dose, however, must be weighed against the additional cost and complexity of developing the drug–carrier combination.

Should one select a minimum acceptable value of therapeutic availability of 10, it is clear from Fig. 2 that drugs with medium or lower total-body clearance values are poor candidates for combination with a drug carrier except when the target blood flow (Q_R) is known to be less than about 3% of the cardiac output. Compounds with high total clearances (40.5% of the cardiac output or more) are better drug-carrier candidates. For therapeutic availability it makes little difference whether or not the clearance at the target site is a significant fraction of the total clearance.

The Drug Targeting Index

High values of the drug targeting index can result when there is a small effective blood flow to the target site coupled with a large total clearance. As Fig. 3 demonstrates, even higher values of DTI are possible whenever there is a large target-site extraction ratio. Drug targeting index values greater than 50 are possible when the drug is significantly cleared by target tissues. In the absence of significant clearance of drug by target tissues, which is the case for most currently available drugs, Eq. (23) dictates that large values of the drug targeting index are possible only when either the total clearance is large or Q_R is very small.

The Nature of the Drug

It is useful to think of any drug as a member of a set of molecules having in common a specific mechanism of action. The set can be divided into two subsets: those that have *in vivo* activity and those that do not because they are precluded from reaching their target sites by a biological barrier. Traditionally, the only means to make use of members of the second set has been to design a molecular modification that moves the molecule from subset two to subset one. In theory, a specially engineered *in vivo* drug carrier could overcome the barrier. The drug-carrier approach, therefore, is an alternate path to the same ideal goal

as molecular modification. The only means available to improve a molecule's performance without either chemical modification or the use of a drug carrier has been to optimize its route of administration and its dosing rate (an excellent example of optimization of methotrexate chemotherapy is given in Ref. 17). The best possible improvement in therapeutic performance may result from carrier-based delivery of the drug to its target sites. However, the therapeutic results obtained by combining the drug with a targeted drug carrier can be indistinguishable from those resulting from optimizing the dosing rate and/or route. Before one decides which approach to take or begins experimental evaluation of a drug–carrier combination, one should obtain the additional information needed to estimate the therapeutic availability and the drug targeting index. Figure 5 was constructed to guide and assist in deciding when a drug will be a good candidate for delivery as a drug–carrier combination, given a minimally acceptable index value. When one considers that no carrier will be 100% efficient at target-site delivery, that the variance of pharmacokinetic parameters within the population for a given drug can be large, and that the variance in the performance properties of a drug carrier will increase the total variance, then having drug targeting index values less than about 5–10 may not offer sufficient promise to warrant development of that drug–carrier combination. On the other hand, if the maximum value is 100, for example, then the drug-carrier approach should be seriously considered.

Suboptimum Targeting of a Drug Carrier

If the drug carrier is not completely locked into the target tissue before drug release occurs, then release will occur elsewhere, i.e., $F_r < 1$, with F_b, F_e and $F_t > 0$. The curves in Fig. 4 show how the drug targeting index changes as delivery at the targets decreases, while being compensated for by release elsewhere. The most logical situation is represented by the curves labeled F_b, where $F_b = 1 - F_r$. As F_r decreases from 1.0 to 0.5, the drug targeting index value declines by at least 60%; the magnitude of such a drop in DTI will approach 50% as the total-body clearance drops to very low values.

Equation (23) states that clearance by tissues originating the toxic effects will contribute to larger drug targeting index values. One might a priori view this prediction as unexpected. However, elimination by the toxicity compartment contributes to the total clearance, and it is because of this that the drug targeting index values increase as $Q_T E_T$ increases. As illustrated in Fig. 4, when the fraction of drug released from the carrier at toxic sites increases from zero, the drug targeting index values can decline sharply from their theoretical maxima. However, as seen in the sequence Figs. 4A, D, E, and F, the magnitude of this decline decreases with increasing blood flow to and clearance by the toxicity compartment.

Another unexpected but interesting lesson is illustrated best in Fig. 4A and results when the fraction of drug release from the carrier that does not occur at the target site occurs instead primarily at the elimination compartment: $F_e = 1 - F_r$. When the drug clearance by the eliminating organs approaches the blood flow to the clearing organ ($E_E \rightarrow 1$), DTI values become relatively insensitive to small changes in F_r when $F_r > 0.5$ but are very sensitive to small changes in F_r when F_r is near zero.

Free-Drug Control Studies

It is generally recognized that changing the route of administration or the dosing rate can alter the therapeutic availability and the therapeutic index. In order to quantify the additional advantage resulting from targeting, as contrasted with an advantage resulting from sustained release, the intravenous free-drug input rate must match the release rates of drug from the drug carrier. Unfortunately, release rates from drug carriers *in vivo* are difficult to determine. The problem could be overcome by comparing relative effectiveness after infusing both the free drug (in one study) and the drug–carrier combination (in another study) until steady state is reached. Because such experimental designs are expensive and technically demanding when feasible, investigators have chosen to compare the pharmacological results following a bolus dose of the drug–carrier combination to the results following a bolus intravenous dose of free drug (e.g., 18–21). This approach has been seen as a means to approximate experimentally the therapeutic advantage of using the drug carrier. Unfortunately the benefits cannot be assigned solely to the carrier's target-site delivery properties when the control study is simply an intravenous dose of free drug,[8] because the intravenous dose rate of free drug would not match the overall drug release rate from the carrier as required by Eq. (9). Given the multiple variables being assessed, experimental strategies that lack such controls may generate little useful information relative to the theoretical approach described here.

Poor Candidate Drugs

Drugs that are good candidates for combination with a targeted drug carrier are unlikely to survive the current drug screening system. Few currently used drugs have significant target-organ extraction ratio or clearance values, and this fact is a necessary consequence of current drug screening practices. The best candidate drug for clinical use is often selected from a set of active molecules having similar mechanisms of action. The most potent member of that set having the least toxicity is preferred. A molecule that has even a modest target-organ extraction ratio will appear to be less potent when it is administered intravenously and compared to a sister molecule having the same inherent potency but no

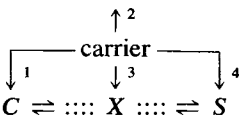
[8] One of the authors has observed (22) that the release rate of model compounds from liposomes following contact with plasma can mimic the ideal intravenous input rate needed to reach quickly and maintain a constant level of drug at a target site. Nathanson *et al.* (17) have calculated the ideal dose rate for methotrexate starting with a model similar to Scheme I. Their report clearly demonstrates that when only an intravenous dose of free drug is used as the experimental control, one cannot assign the entire observed improvement in therapeutic results to improved delivery of drug to targets by the carrier. Release of drug from the carrier before it reaches the target ("sustained release") may also contribute to the observed improvement and, in some cases, may account for all the improvement.

target-organ clearance.[9] As a consequence, the current drug screening system is biased against drugs that would be good candidates for use as drug–carrier combinations. Therapeutic proteins and peptides generally have not been a product of these screens. As a set they tend to have high total clearance values, and so may represent the better candidates.

APPENDIX

Narrowing the Scope of Limitations

Each compartment in Schemes I and II is depicted as being "well stirred," i.e., equilibration of drug within the compartment is fast relative to blood flow. The well-stirred assumption is valid for only a small minority of drugs but greatly simplifies the mathematics. Because of this assumption the AUC_i and C_i values in Eqs. (13) and (20), which refer to the concentration of drug in the i^{th} compartment, can refer to both the concentration at the action site and the compartment's exiting venous concentration. However, in most cases these two concentrations are likely to be quite different! There may also be a considerable time lag before a change in the tissue's blood level concentration is reflected at the action site. Yet, in most such instances Eqs. (13) and (20) will still be valid. To illustrate, let the concentration at an action site be S and the organ's exiting venous concentration be C. Assume that S is related to C by a sequence of transfers that can be described by a set of linear differential equations:



The time course of drug at the two extreme sites will be $C(t)$ and $S(t)$. The Laplace transforms of these two functions are $\tilde{C}(s)$ and $\tilde{S}(s)$, where $\tilde{S}(s) = \tilde{T}(s)\,\tilde{C}(s)$. $\tilde{T}(s)$ is the Laplace transform of the function describing transfer between C and S, $T(t)$. When $s = 0$, $\tilde{S}(0) = \tilde{T}(0)\,\tilde{C}(0)$, which can be rewritten as

$$\int_0^\infty S(t)dt = \tilde{T}(0)\int_0^\infty C(t)dt \tag{24}$$

or

$$AUSC_i = \tilde{T}_i(0)AUC_i \tag{25}$$

Now, consider four examples of drug release from the carrier (illustrated above). In the first example (i) drug is released from the carrier into blood in the target tissue; in the second example (ii) drug is released from the carrier into blood at some site distant from both C and S; in the third example (iii) drug is released at a site X between C and S, where X is characterized by the fact that drug equilibration between C and X is fast relative to equilibration between X and S; in the fourth example (iv) drug is released directly to the action site. In examples i, ii, and iii Eqs. (24) and (25) apply, and the value of $\tilde{T}(0)$ is the same in each case. For example iv, Eq. (24) does not apply and so this example is excluded from current consideration. When $AUSC_i$ values for examples i, ii, and iii are used in place of AUC_i values in Eq. (13), we obtain

$$DTI = \frac{\tilde{T}_r(0)}{\tilde{T}_R(0)} \cdot \frac{\tilde{T}_T(0)}{\tilde{T}_t(0)} \cdot \frac{AUC_r/AUC_t}{AUC_R/AUC_T} \tag{26}$$

because DTI is referenced to the same individual, we expect $\tilde{T}_r(0) = \tilde{T}_R(0)$, and $\tilde{T}_t(0) = \tilde{T}_T(0)$, and so Eq. (26) reduces to Eq. (13). The corresponding expression for TA reduces to Eq. (20). We recognize that there may be situations where the drug release properties of the carrier may alter $\tilde{T}_i(0)$ and that, for some drugs or physiological situations, a nonlinear set of differential equations may be needed to describe $T(t)$, but these exceptions are excluded from this discussion.

The Origin of DTI and TA Terms

The expression for the drug targeting index can be derived in two ways. First, consider steady state. Substitution of Eq. (11) into Eqs. (5)–(8) at steady state gives

$$0 = -(Q_R + Q_E + Q_T)C_b + Q_RC_r + Q_EC_e + Q_TC_t + R_b \tag{27}$$

$$0 = Q_RC_b - \frac{Q_RC_r}{1 - E_R} + R_r \tag{28}$$

$$0 = Q_EC_b - \frac{Q_EC_e}{1 - E_E} + R_e \tag{29}$$

$$0 = Q_TC_b - \frac{Q_TC_t}{1 - E_T} + R_t \tag{30}$$

When Eq. (12) is substituted into each of the above equations and they are then solved for each of the steady-state concentrations, the partial results are

$$C_b = \frac{R_b + (1 - E_R)R_r + (1 - E_E)R_e + (1 - E_T)R_t}{Q_R\Phi} \tag{31}$$

$$C_r = \frac{(1 - E_R)\cdot\Gamma_R}{Q_R\Phi} \tag{32}$$

$$C_t = \frac{(1 - E_T)\cdot\Lambda_R}{Q_R\Phi} \tag{33}$$

where

$$\Gamma_R = R_b + (1 + nE_E + mE_T)R_r + (1 - E_E)R_e + (1 - E_T)R_t \tag{34}$$

$$\Lambda_R = R_b + (1 - E_R)R_r + (1 - E_E)R_e + \left[\frac{E_R}{m} + \frac{nE_E}{m} + 1\right]R_t \tag{35}$$

[9] Consider two hypothetical drugs. One (drug X) is the high-clearance drug from Fig. 4A: $Q_R = 1.25\%$ of the cardiac output or 0.0625 liter/min, $n = 43.2$, $m = 1$, $E_R = E_T = 0.5$, and $E_E = 0.727$. The other (drug Y) is a sister molecule with the same total clearance (40.5% of the cardiac output or 2.025 liters/min) but no response or toxicity compartment clearance ($E_R = E_T = 0$), i.e., $E_E = 0.75$. The value of C_R at steady state is given by $C_R = R_B(1 - E_R)/(E_R + nE_E + mE_T)Q_R$. When equimolar doses of X and Y are given intravenously in their free form ($R_B = 10^{-5}$ mol/min), the resulting steady-state blood levels for X and Y are 2.47×10^{-6} and 4.94×10^{-6} mol/liter, respectively. If all other factors are the same, then drug X is seen as being only 50% as potent as Y.

and

$$\Phi = E_r + nE_E + mE_T \tag{36}$$

Setting Eqs. (1)–(4) equal to zero and solving this set of equations for each dependent variable result in expressions for C_R and C_T at steady state:

$$C_R = \frac{(1 - E_R) \cdot R_B}{Q_R \Phi} \tag{37}$$

$$C_T = \frac{(1 - E_T) \cdot R_B}{Q_R \Phi} \tag{38}$$

Substituting Eq. (9) into Eqs. (32) and (33) and then substituting the results, along with the values for C_R and C_T from Eqs. (37) and (38) into the definition of DTI, Eq. (13), gives an expression for DTI that is the same as Eq. (14):

$$DTI = \frac{\Gamma_F}{\Lambda_F} \cdot \frac{R_o}{R_o} \tag{39}$$

where

$$\Gamma_F = F_b + (1 + nE_E + mE_T)F_r + (1 - E_E)F_e + (1 - E_T)F_t \tag{40}$$

and

$$\Lambda_F = F_b + (1 - E_R)F_r + (1 - E_E)F_e + \left[\frac{E_R}{m} + \frac{nE_E}{m} + 1\right]F_t \tag{41}$$

We now turn to the derivation of DTI in terms of AUC values. The area under the target- and toxicity-site drug concentration curves can be obtained by integrating Eqs. (1)–(8) from time zero to infinity. When this is done, the left-hand side of each equation vanishes, and each concentration C_i is replaced by $\int_0^\infty C_i dt = AUC_i$. Each compartment's drug input rate, R_i, in Eqs. (5)–(8) is replaced by $\int_0^\infty R_i dt = F_i D$, where F_i is the fraction of the drug delivered by the carrier directly to the i^{th} compartment and D is the dose as defined previously. When, in addition, the $k_i V_i$ terms are replaced by the expression in Eq. (11), the results for Eqs. (1)–(3) and (5)–(7) are

$$D - Q_R[(1 + n + m)AUC_B - AUC_R - nAUC_E - mAUC_T] = 0 \tag{42}$$

$$Q_R\left[AUC_B - \frac{AUC_R}{1 - E_R}\right] = 0 \tag{43}$$

$$Q_R\left[mAUC_B - \frac{mAUC_T}{1 - E_T}\right] = 0 \tag{44}$$

$$F_b D - Q_R[(1 + n + m)AUC_b - AUC_r - nAUC_e - mAUC_t] = 0 \tag{45}$$

$$Q_R\left[AUC_b - \frac{AUC_r}{1 - E_R}\right] + F_t D = 0 \tag{46}$$

$$Q_R\left[mAUC_b - \frac{mAUC_t}{1 - E_T}\right] + F_t D = 0 \tag{47}$$

Equations (42), (43), and (44) correspond to Eqs. (1), (2), and (4), respectively. The equation corresponding to Eq. (3) is not shown. Equations (45), (46), and (47) correspond to Eqs. (5), (6), and (8), respectively. Again, the equation corresponding to Eq. (7) is not shown. Solving these two new sets of equations for the two sets of four AUC terms leads to Eqs. (48)–(51).

$$AUC_R = \frac{D(1 - E_R)}{Q_R \Phi} \tag{48}$$

$$AUC_T = \frac{D(1 - E_T)}{Q_R \Phi} \tag{49}$$

$$AUC_r = \frac{D(1 - E_R)\Gamma_F}{Q_R \Phi} \tag{50}$$

$$AUC_t = \frac{D(1 - E_T)\Lambda_F}{Q_R \Phi} \tag{51}$$

Equations for AUC_B, AUC_b, AUC_E, and AUC_e are not needed and so are not listed. Substitution of the AUC values from Eqs. (48)–(51) into the definition of DTI, Eq. (13), gives Eq. (39) with D replacing R_o. Equation (39), in turn, is identical to Eq. (14).

The expression for therapeutic availability at steady state is obtained by substituting the values of C_R and C_r [Eqs. (32) and (37)] into Eq. (20), followed by replacing the R_i terms with $F_i D$ terms according to Eq. (9). The result is

$$TA = \Gamma_F\left(\frac{R_o}{R_B}\right) \tag{52}$$

When R_o for the drug–carrier combination is matched to R_B for the free drug, their ratio equals unity and Eq. (52) reduces to Eq. (21). The expression for therapeutic availability based on the AUC value results from substitution of Eqs. (48) and (50) into Eq. (20), which reduces directly to Eq. (21).

Introducing the Therapeutic Index

The drug targeting index is related to the measure of therapeutic index [Eqs. (17) and (18)] as follows. When the response generated by a dose of free drug in the typical individual correlates best with AUC_R, then there will be a unique value of AUC_R, designated AUC_R^*, associated with MED. We assume that a dose of the drug–carrier combination can generate essentially the same response, as illustrated in Fig. 1, and that the dose required to do so is MED′. That dose will be functionally related to a unique value of AUC_r designated AUC_r^*. Because the response in both cases is the same, we can state that

$$\frac{AUC_R^*}{AUC_r^*} = 1 \tag{53}$$

Substitution of Eqs. (48) and (50) into Eq. (53) gives

$$1 = \frac{AUC_R^*}{AUC_r^*} = \frac{1}{\Gamma_F} \cdot \frac{MED}{MED'} \tag{54}$$

Following the same reasoning, the free drug's MTTD generates both a unique toxicity and AUC_T, designated AUC_T^*. When the drug–carrier combination is administered, the MTTD′ is assumed to generate essentially the same toxicity, which is related to a unique value of AUC_t, designated

AUC_t^*. Because toxicity in both cases is the same we can state that

$$\frac{AUC_T^*}{AUC_t^*} = 1 \tag{55}$$

Substitution of Eqs. (49) and (51) into Eq. (54) gives

$$1 = \frac{AUC_T^*}{AUC_t^*} = \frac{1}{\Lambda_F} \cdot \frac{MTTD}{MTTD'} \tag{56}$$

Multiplication of the inverse of Eq. (56) by Eq. (54) gives

$$\frac{MED \cdot MTTD'}{MED' \cdot MTTD} \cdot \frac{\Lambda_F}{\Gamma_F} = 1 \tag{57}$$

Substitution of the two definitions of therapeutic index, Eqs. (17) and (18), into Eq. (57) followed by rearrangement gives

$$\frac{TI'}{TI} = DTI \tag{58}$$

When response and toxicity correlate best with average or steady-state drug levels, MED will be the minimum effective dose rate and MTTD will be the maximum tolerated toxic dose rate. Therefore, there is a value of R_B in Eq. (37) such that R_B = MED. Similarly, for Eq. (38) there is another value of R_B such that R_B = MTTD. By analogy, there is a value of R_o [from Eq. (9)] in Eq. (32) such that R_o = MED'. Similarly, there is another value of R_o in Eq. (33) such that R_o = MTTD'. It follows that there will be a unique value of C_R at steady state, designated C_R^* and generated by MED, that will be essentially the same as the C_r value at steady state, generated by MED'. Similarly, there will be a unique value of C_T at steady state, C_T^*, generated by MTTD that will be essentially the same as the C_t value at steady state, C_t^*, generated by MTTD'. Because both response and toxicity will be the same in these two cases, we can state that

$$\frac{C_R^*}{C_r^*} = 1 = \frac{C_T^*}{C_t^*} \tag{59}$$

Note that for the steady-state case C_i^* values can be substituted for the corresponding AUC_i^* in Eqs. (54) and (56), which leads directly to the expression for drug targeting index, Eq. (58).

ACKNOWLEDGMENTS

The authors thank Drs. Robert Upton, Thomas Tozer, Valentino Stella, Svein Øie, and Kathleen Giacomini for helpful discussions, and members of the Drug Delivery Group. Georgina Kurtovich provided excellent technical assistance. We thank Andrea Mazel for timely manuscript preparation. Support was provided by Grant GM-24612 from the DHHS and the California Chapter of the American Heart Association.

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