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Research Article

Efficiency of Drug Targeting: Steady-State Considerations Using a Three-Compartment Model

Alan Boddy,[1,3] Leon Aarons,[1] and Karel Petrak[2]

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Physiological models have often been used to investigate the processes involved in drug targeting. Such a model is used to investigate some aspects of drug targeting, including the pharmacodynamics of therapeutic and toxic effects. A simple pharmacodynamic model is incorporated in a three-compartment pharmacokinetic model. Conventional administration and drug targeting are compared at steady state for the same degree of therapeutic effect. The efficiency of drug targeting is quantified as the ratio (TA) of the rates of administration of free drug or of a drug–carrier complex required to achieve this effect. Also, the ratios of drug concentrations in the toxicity compartment (DTI) or of the consequent degree of toxic effects (TI) are used to compare conventional administration with drug targeting. The kinetic characteristics of the drug–carrier complex, rate of elimination, and rate of free drug release, influence TA but not DTI or TI. The importance of these characteristics depends on the cost and toxicity of the drug–carrier complex or of the carrier alone. The pharmacodynamics of the free drug in both the target and the toxicity compartments have an important influence on TI but not on TA or DTI. As the pharmacological selectivity of the drug increases, so does TI. However, a drug with good pharmacological selectivity may not be suitable for drug targeting. TI is also very dependent on the shape of the effect–concentration curves, particularly that for toxicity. While TA increases as the rate of elimination of free drug from either central or target compartments increases, TI may actually be reduced if release of free drug is not confined to the target compartment.

KEY WORDS: drug targeting; site-specific delivery; steady state; pharmacokinetics; pharmacodynamic model.

INTRODUCTION

Drug targeting or site-specific drug delivery involves the systemic administration of drug in an inactive and/or protected form, usually attached to some form of carrier. In this form the drug distributes selectively to those tissues where its presence is associated with a therapeutic effect. Once at the target tissue, free drug is released or activated. This mechanism of drug delivery may overcome problems of delivery of drug to its site of action or of rapid drug elimination. Also, by selectively delivering a drug to its anticipated site of action and minimizing delivery to sites of potential toxicity, drug targeting should improve the ratio of therapeutic to toxic effects.

The current high degree of interest in drug targeting (1–3), has inspired several investigations of the theoretical basis of this approach (4–7). Following this work, we consider how the advantage due to drug targeting is affected by the properties of the drug–carrier, by the pharmacodynamics of the therapeutic and toxic effects of the free drug, and by the pharmacokinetics of the free drug in various situations. Criteria for assessing the advantage or efficiency of drug targeting are also discussed.

THEORETICAL

Throughout this report drug–carrier refers to the conjugate of a drug-targeting carrier and free drug. The carrier without drug attached is assumed to be inert and its fate is not discussed.

The pharmacokinetic model is similar to those used previously (5,6) and is shown in Fig. 1. The volumes of the central, response (target), and toxicity compartments are V_C, V_R, and V_T, respectively. These volumes are assumed to be the same for free drug and drug–carrier. Blood flows to the response and toxicity compartments at rates Q_R and Q_T carrying drug–carrier and free drug at concentrations equal to those in the central compartment. The blood flowing from the compartments carries drug–carrier and drug at concentrations equal to those within the compartments. Free drug can be eliminated from any of the compartments by first-order processes with rate constants K_C, K_R, and K_T. Drug–carrier is eliminated from only the central compartment with a first-order rate constant, K_{DC}. Either free drug or drug–carrier is administered into the central compartment at a constant rate IR_D or IR_{DC}, respectively. The rate of free drug release in the three compartments is assumed to be first

[1] Pharmacy Department, University of Manchester, Oxford Road, Manchester, M13 9PL, Great Britain.
[2] ADDR Unit, Ciba-Geigy Pharmaceuticals, Wimblehurst Road, Horsham, West Sussex, RH12 4AB, Great Britain.
[3] To whom correspondence should be addressed.

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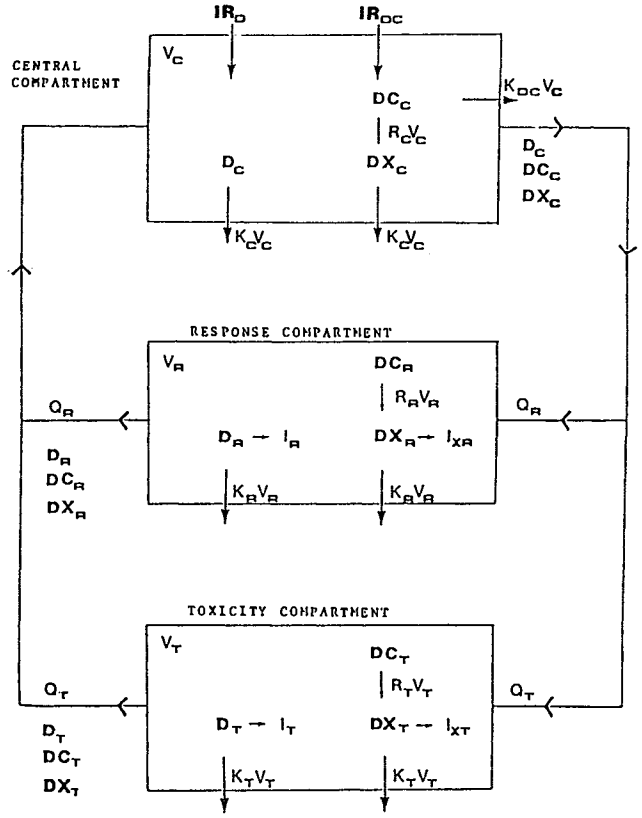

Fig. 1. Three compartment pharmacokinetic model for comparison of drug targeting with conventional administration. Symbols and processes explained in the text.

order with rate constants R_C, R_R, and R_T. When release is confined to the response compartment, R_C and R_T are zero. Rates of elimination and of release of free drug depend on the product of the rate constant and the volume of the compartment. Steady-state concentrations of free drug in the central, response, and toxicity compartments are D_C, D_R, and D_T, respectively. Concentrations of drug–carrier are DC_C, DC_R, and DC_T and concentrations of free drug released from drug–carrier are DX_C, DX_R, and DX_T at steady state.

Differential equations describing the concentrations of drug and drug–carrier can be written, as in previous models of drug targeting (5,6) and regional administration (8). These equations can be solved for steady-state conditions.

During administration of free drug,

$$D_C = IR_D/CL_D \tag{1}$$

$$D_R = \frac{IR_D \cdot Q_R}{CL_D \cdot (Q_R + K_R \cdot V_R)} \tag{2}$$

$$D_T = \frac{IR_D \cdot Q_T}{CL_D \cdot (Q_T + K_T \cdot V_T)} \tag{3}$$

$$\text{where } CL_D = K_C \cdot V_C + \frac{Q_R \cdot K_R \cdot V_R}{(Q_R + K_R \cdot V_R)} + \frac{Q_T \cdot K_T \cdot V_T}{(Q_T + K_T \cdot V_T)} \tag{4}$$

During administration of drug–carrier,

$$DC_C = IR_{DC}/CL_{DC} \tag{5}$$

$$DC_R = \frac{IR_{DC} \cdot Q_R}{CL_{DC} \cdot (Q_R + R_R \cdot V_R)} \tag{6}$$

$$DC_T = \frac{IR_{DC} \cdot Q_T}{CL_{DC} \cdot (Q_T + R_T \cdot V_T)} \tag{7}$$

$$\text{where } CL_{DC} = K_{DC} \cdot V_C + R_C \cdot V_C + \frac{Q_R \cdot R_R \cdot V_R}{(Q_R + R_R \cdot V_R)} + \frac{Q_T \cdot R_T \cdot V_T}{(Q_T + R_T \cdot V_T)} \tag{8}$$

For free drug released from drug–carrier,

$$DX_C = \frac{IR_{DC} \cdot CL_{DX}}{CL_{DC} \cdot CL_D} \tag{9}$$

$$DX_R = \frac{IR_{DC} \cdot Q_R}{CL_{DC}(Q_R + K_R \cdot V_R)} \left[\frac{R_R \cdot V_R}{(Q_R + R_R \cdot V_R)} + \frac{CL_{DX}}{CL_D}\right] \tag{10}$$

$$DX_T = \frac{IR_{DC} \cdot Q_T}{CL_{DC}(Q_T + K_T \cdot V_T)} \left[\frac{R_T \cdot V_T}{(Q_T + R_T \cdot V_T)} + \frac{CL_{DX}}{CL_D}\right] \tag{11}$$

where

$$CL_{DX} = R_C \cdot V_C + \frac{Q_R^2 \cdot R_R \cdot V_R}{(Q_R + R_R \cdot V_R)(Q_R + K_R \cdot V_R)} + \frac{Q_T^2 \cdot R_T \cdot V_T}{(Q_T + R_T\, V_T)(Q_T + K_T \cdot V_T)} \tag{12}$$

The intact drug–carrier conjugate is assumed to be pharmacologically inert. Free drug causes a therapeutic effect (I_R) or toxic effect (I_T) related to concentrations in the response or toxicity compartments by the following pharmacodynamic equations (8):

$$I_R = \frac{D_R^{\gamma R}}{C_{50R}^{\gamma R} + D_R^{\gamma R}} \tag{13}$$

$$I_T = \frac{D_T^{\gamma T}}{C_{50T}^{\gamma T} + D_T^{\gamma T}} \tag{14}$$

I_R and I_T are fractions of maximal effect in the two compartments, C_{50R} and C_{50T} are concentrations of drug causing 50% of maximal therapeutic or toxic effects, and the shape of the effect–concentration curve is controlled by γ_R and γ_T. Figure 2 is a plot of I against D/C_{50}. For the analogous equations for drug released from drug–carrier D_R and D_T are replaced by DX_R and DX_T, with IX_R and IX_T replacing I_R and I_T.

For a required degree of therapeutic effect, the necessary concentration in the response compartment can be calculated by solving Eq. (13) for D_R and DX_R. The rates of input of free drug or of drug–carrier needed to maintain this concentration can be calculated by solving Eqs. (2) and (10) for IR_D and IR_{DC}. The resultant concentrations of free drug in the toxicity compartment, D_T and DX_T, can be calculated from Eqs. (3) and (11). The consequent fractions of maximum toxic effect, I_T and I_{XT}, are calculated by inserting these concentrations into Eq. (14).

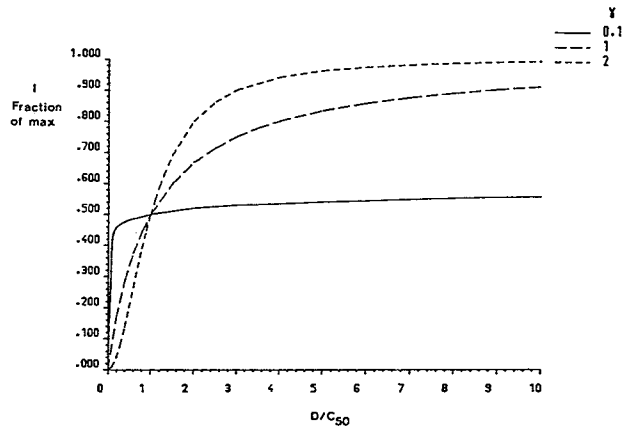

Fig. 2. Plot of fraction of maximal effect against concentration relative to C_{50} for γ less than, equal to, and greater than unity.

Therapeutic availability (TA) can be defined as the ratio of the rate of input of free drug to that of drug–carrier for the same degree of maximal therapeutic effect [Eq. (15)]. A drug-targeting index (DTI) has been previously defined as the ratio of concentrations in the response and toxicity compartments when a drug–carrier is administered divided by the same ratio when free drug is administered (5). When the concentrations in the response compartment are identical, DTI is equal to the ratio of concentrations in the toxicity compartment. A similar targeting index (TI) can be defined by substituting toxic effects for concentrations in the toxicity compartment [Eq. (17)].

$$\mathrm{TA} = \frac{IR_D}{IR_{DC}} \tag{15}$$

Substituting for IR_D and IR_{DC} yields

$$\mathrm{TA} = \frac{CL_D \cdot R_R \cdot V_R}{CL_{DC}(Q_R + R_R \cdot V_R)} + \frac{CL_{DX}}{CL_{DC}} \tag{16}$$

$$\mathrm{TI} = \frac{I_T}{I_{XT}} \tag{17}$$

Substituting for I_T and I_{XT} yields

$$\mathrm{TI} = \frac{\left[\frac{C_{50T}}{C_{50R}}\right]^{\gamma_T}\left[\frac{CL_R}{CL_T}\right]^{\gamma_T} + \left[\frac{Q_{T'}}{Q_{R'}}\right]^{\gamma_T}\left[\frac{I_R}{1-I_R}\right]^{\gamma_T/\gamma_R}}{\left[\frac{C_{50T}}{C_{50R}}\right]^{\gamma_T} + \left[\frac{Q_{T'}}{Q_{R'}}\right]^{\gamma_T}\left[\frac{I_R}{1-I_R}\right]^{\gamma_T/\gamma_R}} \tag{18}$$

where

$$CL_R = \frac{R_R \cdot V_R}{Q_R + R_R \cdot V_R} + \frac{CL_{DX}}{CL_D}$$

$$CL_T = \frac{R_T \cdot V_T}{Q_T + R_T \cdot V_T} + \frac{CL_{DX}}{CL_D}$$

$$Q_{R'} = \frac{Q_R}{Q_R + K_R \cdot V_R}$$

$$Q_{T'} = \frac{Q_T}{Q_T + K_T \cdot V_T}$$

When release is absolutely selective for the response compartment ($R_C = R_T = 0$), drug is eliminated from only the central compartment ($K_R = K_T = 0$) and pharmacodynamic parameters are equal in the two compartments with a normal I_{MAX} model ($\gamma_R = \gamma_T = 1$):

$$\mathrm{TA} = \frac{K_C \cdot V_C + Q_R}{\{[Q_R(K_{DC} \cdot V_C + R_R \cdot V_R)]/R_R \cdot V_R\} + K_{DC} \cdot V_C} \tag{19}$$

$$\mathrm{TI} = \frac{K_C \cdot V_C(1 - I_R)}{Q_R} + 1 \tag{20}$$

As I_R tends toward zero, effect rises linearly with concentration and TI becomes identical to DTI. Also, when both Q_R and $R_R \cdot V_R$ are much greater than $K_{DC} \cdot V_C$, TA equals DTI.

Conventional administration and drug targeting are compared at different fractions of the maximum therapeutic response. The advantage due to drug targeting is assessed under different conditions by varying one parameter while holding the others constant (values in Table I). Unless stated otherwise, free drug release is assumed to be absolutely selective for the response compartment.

RESULTS

From Eq. (20) it can be seen that TI and DTI are maximized by a drug which is rapidly eliminated (high K_C) and targeted to a site with low blood flow (Q_R). Another important characteristic is the rate of elimination from the target site (rate constant K_R). Both indices increase as K_R is increased. The influence of these characteristics on the advantage of drug targeting, prodrugs, or regional administration

Table I. Standard Values Used for Pharmacokinetic and Pharmacodynamic Parameters of the Three-Compartment Model[a]

Parameter	Value	Comment
V_C	40 liters	Volume of total body water
V_R	0.4 liter	
V_T	0.4 liter	Response and toxicity compartments equal
Q_R	0.5 liter hr^{-1}	Small fraction of cardiac output
Q_T	0.5 liter hr^{-1}	Response and toxicity compartments equal
K_{DC}	0.05 hr^{-1}	Slow elimination
K_C	0.5 hr^{-1}	High relative to K_{DC}
K_R	0	No elimination in response compartment
K_T	0	No elimination in toxicity compartment
C_{50R}	1	
C_{50T}	1	Therapeutic and toxic effects equally sensitive to drug
γ_R	1	
γ_T	1	Ordinary I_{MAX} model with no sigmoidicity
R_R	100 hr^{-1}	Release rapid relative to other processes
R_T and R_C	0	Release confined to response compartment

[a] Units as stated in the table, units of concentration, and C_{50} values are arbitrary.

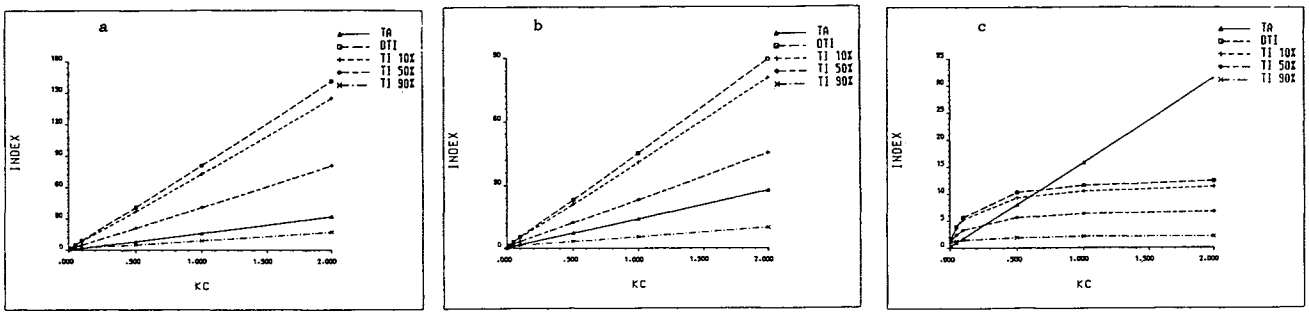

Fig. 3. Plot of targeting indices (TA, DTI, and TI at 10, 50, and 90% of maximum therapeutic response) against the rate constant for elimination from the central compartment when release occurs in (a) response compartment alone (R_R = 100 hr^{-1}), (b) response and central compartments (R_C = 0.01 hr^{-1}), and (c) response and toxicity compartments (R_T = 0.1 hr^{-1}).

over conventional administration has been noted previously (5–11). This influence is not dealt with here, except where deviations from previous assumptions occur.

Characteristics of the Drug–Carrier Complex

The advantage due to drug targeting, quantified by either DTI or TI, is independent of the rate constants for free drug release or for elimination of drug–carrier. Neither of these parameters influences the pharmacokinetics of the free drug at steady state. However, the efficiency of drug targeting (TA) is sensitive to changes in either of these parameters. Both affect the rate at which drug–carrier must be introduced into the system to maintain a given concentration in the response compartment. Thus, TA increases either as R_R increases or as K_{DC} decreases, reaching a limiting value at high values of R_R.

Elimination of the Free Drug in Central and Response Compartments

As mentioned above the influence of elimination of free drug either from the response site or after returning to the central compartment has been examined previously. It has been suggested that drug elimination from the response site is highly desirable if a significant advantage is to be achieved by drug targeting (5). However, the effect on DTI and TI of increasing the rate of elimination from these compartments changes if free drug is released from the drug–carrier outside of the response compartment.

Increasing K_C increases all of the indices when free drug release occurs in only the response (Fig. 3a) or response and central (Fig. 3b) compartments. When release occurs in both the response and the toxicity departments (Fig. 3c) TA is still proportional to K_C, but DTI and TI do not increase when K_C is increased above a certain value.

The benefits of elimination directly from the target site can be seen for DTI when release of free drug is confined to that site (Fig. 4a). The increase in TI with increasing K_R is less dramatic, especially for a high degree of therapeutic effect. When release of free drug also occurs in the central (Fig. 4b) or toxicity (Fig. 4c) compartments, the gain in DTI with increasing K_R is reduced and TI actually decreases. This reversal of the influence of increasing K_R is because IR_{DC} must be increased to maintain the therapeutic effect as drug is lost more rapidly from the target site. Increasing IR_{DC} increases the concentration of drug–carrier and rate of release of free drug in the toxicity compartment. Owing to the shape of the effect–concentration curve, I_{XT} increases more than I_T so that TI is reduced.

Thus, characteristics which appear to optimize drug targeting when release is confined to the response compartment may have little or the opposite effect when drug release is less than absolutely selective. The rate constants used (R_R = 100, R_C = 0.01, and R_T = 0.1) give rates of release in the response compartment 100 times that in the central compartment or 1000 times that in the toxicity compartment. Also, the influence of a parameter on the advantage of drug targeting may be different depending on whether the index chosen is based on concentrations or on effects. The pharmacodynamics of both therapeutic and toxic effects should, therefore, be considered.

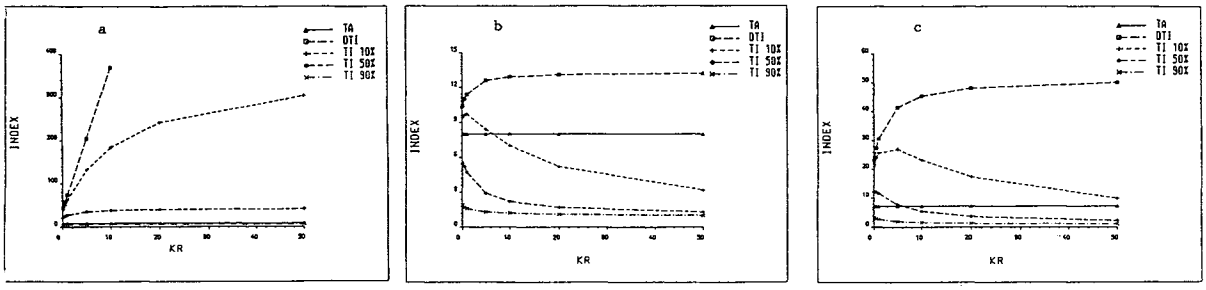

Fig. 4. Plot of targeting indices (TA, DTI, and TI at 10, 50, and 90% of maximum therapeutic response) against the rate constant for elimination from the response compartment when release occurs in (a) response compartment alone (R_R = 100 hr^{-1}), (b) response and central compartments (R_C = 0.01 hr^{-1}), and (c) response and toxicity compartments (R_T = 0.1 hr^{-1}).

Pharmacodynamics

Equations (18) and (20) indicate that TI decreases as the fraction of maximum therapeutic effect (I_R) increases. This is due to the shape of the effect–concentration curve in the pharmacodynamic model used (Fig. 2). With γ values equal to unity, the sensitivity of toxic and therapeutic effects to changes in concentration decreases as the concentration is increased. Concentrations of free drug in the response compartment (and therapeutic effects) are equal during the two modes of administration. However, the concentration of free drug in the toxicity compartment during drug–carrier administration should be less than that during conventional administration. Thus, the magnitude of the toxic effect during drug targeting is more sensitive to changes in concentration and I_{XT} increases more than I_T as the magnitude of the therapeutic effect is increased. This behavior has been noted previously in a theoretical investigation of arterial administration (10).

The values of the pharmacodynamic parameters have no influence on TA or on DTI. However, a drug with a high C_{50R} will require a high rate of input of drug–carrier to maintain a given degree of therapeutic effect.

Relative Sensitivities of Therapeutic and Toxic Effects

The sensitivity of an effect to drug concentration is determined by the C_{50} value. Figure 5 shows how TI varies with the ratio of C_{50R} to C_{50T}. Drug targeting may be inappropriate for a drug which has a high degree of pharmacological selectivity. However, targeting such a drug appears to provide a greater advantage over conventional administration than targeting a poorly selective drug.

Shape of the Effect–Concentration Relationship for Therapeutic Response and Toxicity

The shape of the relationship between effect and concentration is determined by the value of γ_R and γ_T. When the degree of therapeutic effect is low, TI increases with increasing γ_R (Fig. 6). When the degree of therapeutic effect is high, TI decreases with increasing γ_R. Although TA is independent of γ_R, the required rate of input of drug–carrier increases dramatically as γ_R exceeds unity.

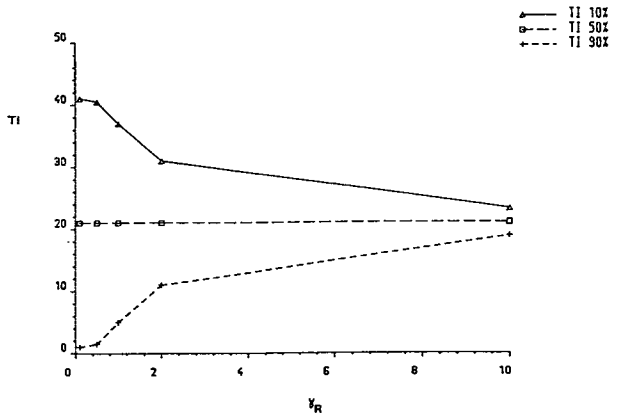

Fig. 6. Plot of targeting index (TI at 10, 50, and 90% of maximum therapeutic response) against the sigmoidicity coefficient for therapeutic effect (γ_R).

The value of TI increases with increasing γ_T, especially when γ_T is greater than one (Fig. 7). A similar increase in TI is observed if γ_R and γ_T are increased together (Fig. 8).

DISCUSSION

A three-compartment model was used to determine the influence of different characteristics of the drug–carrier, free drug, and pharmacodynamics of therapeutic and toxic effects on the advantage of drug targeting over conventional administration. Also, the magnitude of the rate of input of drug–carrier was used to judge the impact of different factors on the practicability of drug targeting.

At steady state, the rates of elimination and cleavage of drug–carrier complex have no influence on the advantage due to drug targeting. These rates must, however, be considered if therapeutic drug concentrations are to be achieved with realistic input rates of drug–carrier. Increases in the rates of elimination of free drug, from either central or response compartments, tend to increase the advantage due to drug targeting but also increase the required rate of input of drug–carrier to maintain a therapeutic effect.

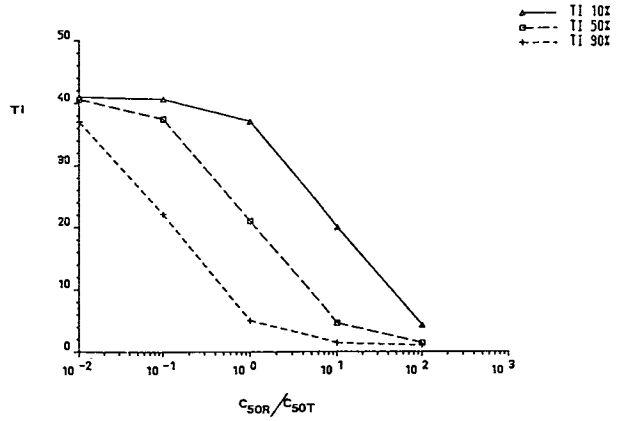

Fig. 5. Plot of the targeting index (TI at 10, 50, and 90% of maximum therapeutic response) against the log of the ratio of C_{50} values for therapeutic and toxic effects.

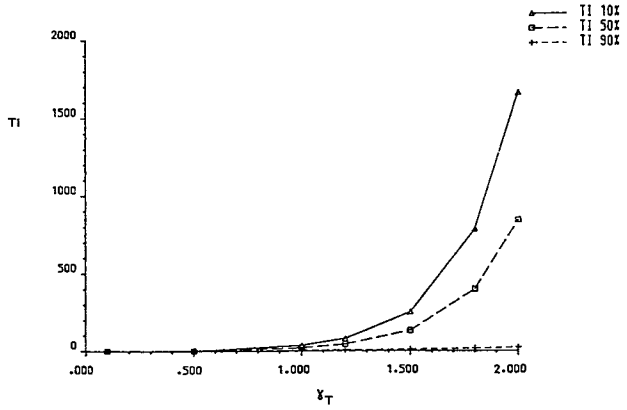

Fig. 7. Plot of targeting index (TI at 10, 50, and 90% of maximum therapeutic response) against the sigmoidicity coefficient for toxic effect (γ_T).

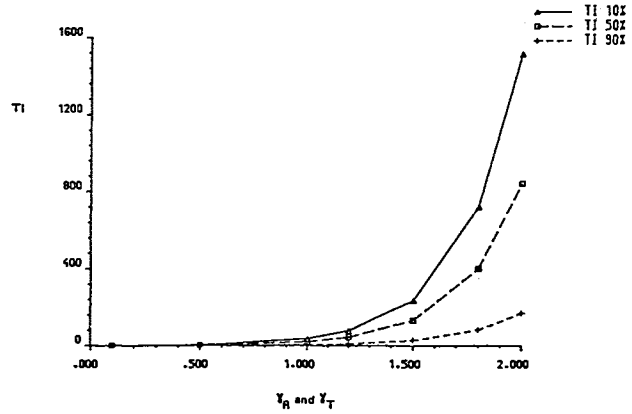

Fig. 8. Plot of targeting index (TI at 10, 50, and 90% of maximum therapeutic response) against the sigmoidicity coefficients for both therapeutic and toxic effects ($\gamma_R = \gamma_T$).

The influence on targeting indices (5) or on pharmacokinetic advantage (6,8,10,11) of elimination from central and response compartments and of flow to the response compartment has been noted previously. It was demonstrated in the present investigation that the increase in targeting advantage gained by increasing the elimination rates may be reversed or even become a loss if release of free drug was not confined to the response compartment.

The influence of pharmacodynamics on the advantage due to drug targeting has not been considered previously. The pharmacodynamic model used in the present investigations was relatively simple yet illustrates the point that the relationship between effect and concentration at both response and toxicity sites should be considered. For the simple I_{MAX} model ($\gamma_R = \gamma_T = 1$) the lower toxic effect subsequent to drug targeting was more sensitive to changes in concentration than the toxic effect after conventional administration. Thus, as the required degree of therapeutic effect increases, the advantage due to drug targeting decreases. The selectivity of the drug with regard to toxic and therapeutic effects was important, but it may be inappropriate to target a drug with inherently high pharmacological selectivity. The influence of the shape of the effect–concentration relationships was also important, particularly the threshold-type phenomenon for toxic effects when γ_T was greater than one.

The aim of the present work was to investigate the conditions under which drug targeting was most likely to succeed and how to optimize the characteristics of drug–carrier or choice of free drug. It was not intended to provide a definitive and absolute evaluation of a particular combination of drug–carrier, drug, and disease state but to allow for discrimination among more or less suitable candidates for the components of a successful drug–targeting system. The use of pharmacokinetic models to predict quantitatively the therapeutic advantage due to drug targeting requires more information on physiology, anatomy, pathology, pharmacokinetics, and pharmacodynamics than is presently available for most systems.

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REFERENCES

1. G. Gregoriadis, G. Poste, J. Senior, and A. Trouet (eds.). *Receptor-Mediated Targeting of Drugs* (NATO ASI, Series A, Life Sciences, Vol. 82), Plenum Press, New York, 1984.
2. E. Tomlinson. *Adv. Drug. Deliv. Rev.* 1:87–198 (1987).
3. J. Robinson and V. H. L. Lee (eds.). *Controlled Drug Delivery: Fundamentals and Applications,* Marcel Dekker, New York, 1987.
4. V. J. Stella and K. J. Himmelstein. In R. T. Borchardt, A. J. Repta, and V. J. Stella (eds.), *Directed Drug Delivery,* Humana Press, New York, 1985, pp. 247–267.
5. C. A. Hunt, R. D. MacGregor, and R. A. Siegel. *Pharm. Res.* 3:333–344 (1986).
6. J. F. M. Smits and H. H. W. Thijssen. In H. A. J. Struyker-Boudier (ed.), *Rate-Controlled Drug Administration and Action,* CRC Press, Boca Raton, Fla., 1986, pp. 83–114.
7. G. Levy. *Pharm. Res.* 4:3–4 (1987).
8. R. L. Dedrick. *J. Pharm. Sci.* 75:1047–1052 (1986).
9. N. H. G. Holford and L. B. Sheiner. *Pharmacol. Ther.* 16:143–166 (1982).
10. W. W. Eckman, C. S. Patlak, and J. D. Fenstermacher. *J. Pharmacokinet. Biopharm.* 2:257–285 (1974).
11. S. Øie and J.-D. Huang, *J. Pharm. Sci.* 70:1344–1347 (1981).