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A Critical Evaluation of the Principles Governing the Advantages of Intra-arterial Infusions

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From the literature, there appears to be inadequate evidence supporting the clinical use of intra-arterial infusions as a method of drug administration. This problem has been evaluated with consideration of the advantages gained in increased total drug delivery and increased drug effectiveness in the region supplied by the infused artery and consideration of the advantage of reduced systemic drug delivery following intra-arterial infusion. Carefully chosen simplifying assumptions allow precise determination of the advantages of regional or systemic drug delivery when drug delivery is evaluated by the total time integral of drug concentration. Simplified experimental approaches are suggested for the precise measurement of these advantages. Drug effectiveness is more difficult to evaluate because of the usual nonlinear relationship between effect and concentration. However, certain relationships between the advantage of regional drug delivery and the advantage of regional drug effects are elucidated. This analysis offers new insight into the factors which determine the value of intra-arterial drug administration and hopefully will help guide both future experimental studies in this area and clinical application of this method.

KEY WORDS: arterial infusions; venous infusions; drug administration; nonlinear effects; injection site advantages; drug delivery.

INTRODUCTION

Intra-arterial infusion has been used frequently as a special means of drug administration. The major clinical application of this technique is in the field of cancer chemotherapy, but it has also been used in clinical pharmacology studies of localized vascular responses in various organs such as the brain and has been widely used in nonclinical experimental studies. Those who have conducted these studies have assumed that intra-arterial infusion of drugs offered two distinct advantages over more common systemic routes

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of administration such as intravenous infusion. These are (a) that arterial infusion provides increased drug delivery to the area supplied by the infused artery and (b) that arterial infusion results in delivery of an *appreciably* reduced dosage of drug to the systemic circulation. Despite the apparent acceptance of these assumptions, there does not seem to be an adequate theoretical or experimental justification for them in the literature.

Several studies using experimental animals and humans have been designed to test the first assumption. Many of these are clinical cancer chemotherapy studies which enthusiastically claim proof of it. However, these claims are open to serious objections in that they do not directly compare intra-arterial and intravenous administration, consist almost entirely of subjective evaluations, and do not allow valid statistical treatment of these evaluations. Among specific experimental studies, Klopp *et al.* (1) showed striking local effects after arterial infusion of nitrogen mustard, but they did not quantitate their results or experimentally compare these results to those with venous infusion. Jinnai *et al.* (2) and Liguori *et al.* (3) stated that arterial infusion resulted in higher drug concentrations in areas which were supplied by the infused artery compared to areas which were supplied by other arteries. Clarkson and Lawrence (4), using the same type of comparison, found conflicting results, and they were unable to validate the advantage of arterial infusion. However, this type of study does not provide valid comparisons between arterial and venous routes of infusion because the total dose delivered to the systemic circulation may have been less than that which was infused into the artery. Of the studies in which tissue levels were measured after both arterial and venous infusions, Ohshiro (5) and Liguori *et al.* (3) were unable to show a difference between the two routes, while Yamada *et al.* (6) and Hayakawa *et al.* (7) showed increased tissue levels after arterial infusion. Norrell and Wilson (8) demonstrated a longer survival after carotid artery infusion of vinblastine than after venous infusion in a group of rats which had received an intracerebrally implanted tumor. This is the only study where the total effect of drug administration was evaluated and the only study which clearly supports the first assumption.

There is also considerable disagreement in the literature over the magnitude of the advantage which can be gained by arterial infusion. Owens and Hatiboglu (9) calculated that internal carotid artery infusion should result in concentrations 10–15 times greater than those expected from intravenous administration. However, experimental measurement of this advantage ranged from slight (6,8) to a maximum of about 2 times the level achieved by venous infusion (7).

Other than the clinical cancer chemotherapy studies alluded to above, there do not appear to be any experiments which have specifically evaluated

the second assumption, i.e., reduced drug delivery to the systemic circulation, or any estimate of the possible magnitude of this assumed advantage.

It is true that some advantage of increased regional drug delivery or decreased systemic drug delivery will be gained by arterial infusion in almost all cases. However, these advantages may be so small in certain situations that there is no practical benefit from the use of this method of drug administration. In a clinical setting, there are a number of problems involved with the use of arterial infusions. There is usually greater risk to the health of the patient from such complications as embolization, arterial occlusion, and excessive regional drug toxicity, and costs are increased due to a greater requirement for professional services and hospitalization. Therefore, it would seem essential that the use of arterial infusions should be based on quantitative evaluation of the advantages to be gained. The purpose of this paper is to explore by mathematical analysis the fundamental principles of circulation, blood–tissue exchange, and pharmacology which govern the magnitude of these potential advantages.

ANALYSIS

At the present time, it is impossible to formulate a general approach which can handle all possible situations. Because of this, it was decided to initially approach this problem by evaluating the tissue concentrations of drug achieved by respective arterial and venous infusions and to evaluate total drug delivery to a site by the integral of drug concentration at that site over the whole time that drug is present. The major assumption in this analysis is that drug distribution within the body can be described by a linear compartmental model with constant rate coefficients. Although this will not be appropriate to all drugs and to all systems, it will be appropriate in some cases. From this analysis, it will be possible to make specific statements about the principles which govern the advantages of increased regional drug delivery and decreased systemic drug delivery after arterial infusion.

This information can then be directly applied to the evaluation of drug effects when effects are directly proportional to concentration. When concentration–effect relationships are nonlinear, however, evaluation of the advantage of increased drug effects from arterial infusion is more difficult.

With the assumption that concentration–effect curves do not vary over time, it is possible to make reasonable approximations of the applicability of increased regional drug delivery to the advantage of increased drug effects resulting from arterial infusion for drugs with known concentration–effect relationships.

While all the problems of evaluating the benefits of arterial infusion will not be dealt with, this paper serves as an initial attempt to formulate

the problems and reveal the complexities involved. It is hoped that this mathematical analysis will form a foundation on which further experimental and theoretical work can build.

ASSUMPTIONS

First, it is assumed that the kinetics of drug distribution within the body can be effectively represented by linear compartmental analysis. This simply implies that these kinetics can be described through the use of a certain noninfinite number of compartments.

The second assumption is that the rate coefficients which describe circulation of the blood, blood–tissue exchange, and drug loss remain constant over the complete range of drug concentrations and throughout the time periods involved.

Finally, in order to simplify this analysis, it was decided to consider drug delivery to regions which receive blood solely from the artery being evaluated for infusion.

FACTORS INFLUENCING THE ADVANTAGE OF REGIONAL DRUG DELIVERY BY ARTERIAL INFUSION

Having chosen to evaluate drug delivery to a site by the integral of the drug concentration over time, a convenient way to compare the respective integrals achieved at that site after arterial and venous infusion must be found. In order to do this, a simple compartmental model was chosen as a means of illustration. The oversimplification of the process represented by the model is readily apparent; however, the principles which are illustrated are valid in general, as will be shown.

Relationship of Time Integrals of Arterial and Tissue Concentrations

Figure 1 presents this simple model of drug exchange between a specific site (compartment 2) and its adjacent capillary blood (compartment 1). Drug entry into the model is represented by a function $C_0(t)$ which corresponds to the level of drug at any time (t) in the arterial blood perfusing an organ. Throughout this paper, the function $C_0(t)$ will represent the arterial amount of drug upstream from the site at which arterial infusion is being evaluated. Where necessary, distinction will be made between the arterial function obtained by intravenous infusion, $[C_0(t)]_{\text{venous}}$, and that obtained by intra-arterial infusion, $[C_0(t)]_{\text{arterial}}$. The rate of tissue blood flow divided by the volume of compartment 1 is k_1, whereas k_2 is the reciprocal of the mean transit time for the capillary blood. The capillary perme-

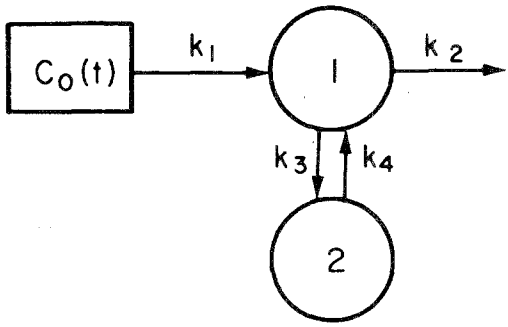

Fig. 1. Simplified model of drug exchange between a specific tissue site (compartment 2) and its adjacent capillary blood (compartment 1). $C_0(t)$ is the input function representing arterial concentration.

ability coefficients, tissue–blood partition coefficients, and other parameters of exchange between capillary blood and tissue are represented by k_3 and k_4. If the amounts of drug in compartments 1 and 2 are expressed as C_1 and C_2, respectively, simple differential equations may be written for each:

$$dC_1/dt = k_1C_0(t) + k_4C_2 - (k_2 + k_3)C_1 \tag{1}$$

and

$$dC_2/dt = k_3C_1 - k_4C_2 \tag{2}$$

Realizing that the amount of drug (C_i) in any compartment (i) within the model is 0 at $t = 0$ and returns to 0 at $t = \infty$, equations 1 and 2 may be integrated from $t = 0$ to $t = \infty$ to yield

$$\int_0^\infty C_2\,dt = (k_1k_3/k_2k_4)\int_0^\infty C_0(t)\,dt \tag{3}$$

This relationship states that the integral of the amount of drug present at any site in a tissue is proportional to the integral of the amount of drug in the arterial blood which is perfusing that tissue. Furthermore, equation 3 is general since for any number of compartments (n) there will be n simultaneous equations which may be solved in an analogous manner to that used above. As proven in Appendix I, this yields

$$\int_0^\infty C_i\,dt = k_i'\int_0^\infty C_0(t)\,dt \tag{4}$$

where k_i' represents the combined coefficients which are involved with exchange of drug within the system for compartment i.

Equation for the Advantage of Regional Drug Delivery

In order to quantitate the delivery advantage to a particular site (b) resulting from arterial infusion, R_d is defined as the ratio of the total drug delivery after arterial infusion to that after venous infusion:

$$R_d = \left[\int_0^\infty C_b(t)\,dt\right]_{\text{arterial}} \Big/ \left[\int_0^\infty C_b(t)\,dt\right]_{\text{venous}} \tag{5}$$

Substituting equation 4 into equation 5 and canceling k_b' from the numerator and denominator yields

$$R_d = \left[\int_0^\infty C_0(t)\,dt\right]_{\text{arterial}} \Big/ \left[\int_0^\infty C_0(t)\,dt\right]_{\text{venous}} \tag{6}$$

Thus the advantage of increased drug delivery resulting from arterial infusion is determined solely by factors which influence the time integrals of the arterial drug levels obtained, respectively, by arterial and venous infusion.

R_d Dependent on a Single Probability

It is now possible to evaluate the factors which influence R_d. The arterial function $C_0(t)$ is determined by the number of drug molecules which are present in that artery at any time. One can distinguish between those molecules which are making their first appearance in that artery and those which are returning after having once passed through the same artery. The average number of appearances in the artery for a drug molecule which has entered the artery for the first time will be represented as θ. Therefore, each molecule of drug which enters the infused artery at least one time will appear in that artery an average of θ times. The total number, N_t, of drug molecule entries, independent of whether it is the initial entry or a reentry, into that artery over the time that drug is present in the body is then dependent on the number, N_0, of drug molecules which enter the artery at least one time in the following manner:

$$N_t = N_0\theta \tag{7}$$

If F is the flow of blood through the artery being infused and N_A is Avogadro's number, then

$$N_t = FN_A \int_0^\infty C_0(t)\,dt \tag{8}$$

Equations 7 and 8 may be inserted into equation 6 and terms rearranged to give

$$R_d = [N_0]_{\text{arterial}}/[N_0]_{\text{venous}} \tag{9}$$

Of the total number of drug molecules injected (N_i), all will make an initial appearance in the artery after intra-arterial infusion ($[N_0]_{\text{arterial}} = N_i$), but only a fraction ($\beta$) of them will enter the artery being considered after intravenous infusion ($[N_0]_{\text{venous}} = \beta N_i$). Therefore, inserting these relationships into equation 9 yields

$$R_d = 1/\beta \tag{10}$$

Equation 10 indicates that the advantage of regional drug delivery is determined by the probability that an intravenously injected drug molecule will enter the arterial site being evaluated at least once after injection. The probability for a molecule to enter an artery at least one time is independent of the parameters of drug distribution and loss within the region supplied by that artery. Equation 10 shows, therefore, that parameters of drug exchange and drug loss (tissue blood flow, capillary permeability, binding, partition coefficients, etc.) within the region supplied by the infused artery do not influence R_d. Parameters of drug distribution and drug loss outside of this region will have a major influence on this advantage because they determine β. If there is no loss of drug outside of this region, then $\beta = 1$ and $R_d = 1$ (no advantage). A formal proof of the above discussion is presented in Appendix II.

It is clear that the probability (β) that intravenously injected drug will enter the infused artery at least once is influenced to a great degree by the fraction of drug which enters this artery during the first passage through the systemic circulation and also by the number of times that each molecule of drug recirculates systemically. However, because of the complexity of factors which influence β, and because it has a value which is virtually impossible to determine, more practical approaches are needed to determine the magnitude of R_d.

R_d Independent of Rate of Infusion

In order to quantitatively evaluate R_d, it is necessary to first understand that this advantage is not dependent on the rate of drug infusion. While the formal proof of this is presented in Appendix III, it is possible to discuss this intuitively. Since for a linear system each drug molecule can be considered to distribute in the body independently of every other molecule, each molecule will have a given probability of appearing at a certain site in the body and of remaining in that site for a certain period of time. Because

these probabilities determine the integral of the amount of drug in that site, this integral will not vary if the molecules are injected singly (slow infusion) or if all the molecules are injected together (bolus infusion). This, of course, is true only if one compares injections at a single site and the total number of molecules is the same in each case. Since changes in the rate of infusion at a single injection site do not change the total integral of drug levels at another site, the advantage of drug delivery by arterial infusion is independent of the rate of infusion.

Two Methods for Experimental Determination of the Value of R_d

It will now be shown that R_d may be experimentally determined for a single bolus injection of drug. The fundamental point to realize is that the advantage gained by arterial infusion is established during the first passage of drug through the area being supplied by the infused artery. After the first passage, the drug returns to the systemic circulation and is distributed as though it were injected intravenously.

From Fig. 2, it is seen that after a single bolus injection the integral $\int_0^\infty C_0(t)\,dt$ can be divided into two components. After injection, a rapid rise and fall of $C_0(t)$ will occur due to the first passage of injected drug through the artery. Let I_a represent the integral of $C_0(t)$ for the first passage of drug after arterial infusion and I_v represent the integral of $C_0(t)$ for the first passage of drug through the arterial blood after venous infusion. In this case, I_v is determined during the first passage of the bolus through the whole systemic circulation (it does not refer to the first passage of each molecule through the artery being evaluated as was the case in the previous analysis involving β). Following the first bolus, $C_0(t)$ again rises and falls more slowly due to systemic recirculation of drug. The integral of the portion of $C_0(t)$ due to recirculating drug, which will be called the "recirculation integral," will be designated I_{ra} for intra-arterial infusion and I_{rv} for intravenous infusion. Equation 6 may now be expressed as

$$R_d = (I_a + I_{ra})/(I_v + I_{rv}) \tag{11}$$

Each of these terms can be related, in the following way, to the total dose of drug injected. From the Stewart–Hamilton principle, I_a = total dose/flow (F) through the infused artery and I_v = total dose/cardiac output (C.O.).[3]

Define ϕ_i as I_{ri}/total dose, where $i = a, v$. Thus ϕ is equivalent to the recirculation integral when $C_0(t)$ is expressed as fraction of total dose per

[3]This assumes no loss of drug from the lungs during the first passage after intravenous infusion. If there were such loss, the expression would be $I_v = (1 - \delta_l) \cdot (\text{total dose})/(\text{C.O.})$, where δ_l is the fraction of total dose lost during first passage through the lungs.

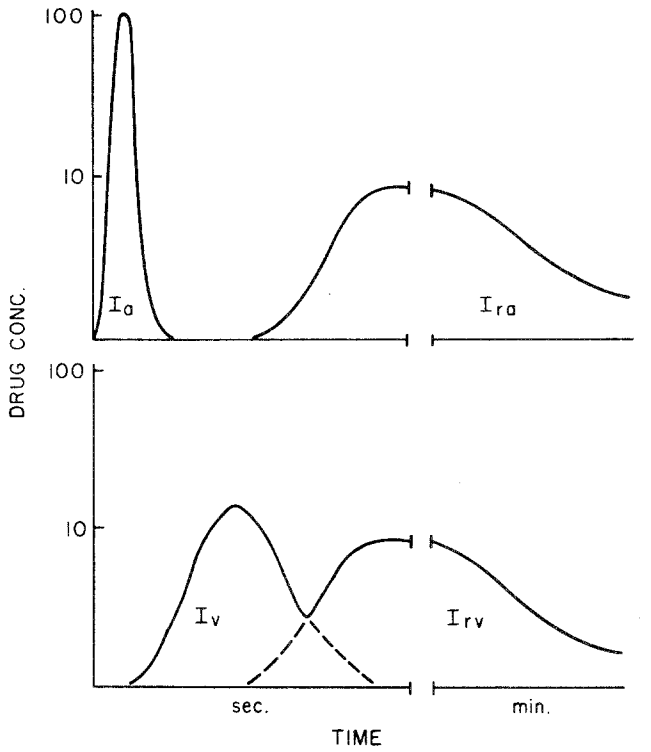

Fig. 2. Representation of arterial concentration curves following bolus injections of drug by intra-arterial (a) and intravenous (v) routes, respectively.

liter of blood and its units are min · liter^{-1}. If there is no loss of drug from the lungs, equation 11 can be expressed as

$$R_d = \frac{1 + [\alpha(\text{C.O.})\phi_a]}{\alpha + [\alpha(\text{C.O.})\phi_v]} \tag{12}$$

where $\alpha = F/\text{C.O.}$, which is the fraction of the cardiac output which flows through the artery being infused. If there is loss of drug from the lungs, equation 12 becomes

$$R_d = \frac{1 + [\alpha(\text{C.O.})\phi_a]}{\alpha(1 - \delta_l) + [\alpha(\text{C.O.})\phi_v]} \tag{13}$$

Therefore, the advantage of drug delivery to a particular site by infusion into the artery which perfuses that site can be determined by the absolute value for cardiac output, the fraction of the cardiac output which

distributes to that artery, and the recirculation integrals which are characteristic of the drug. Equations 12 and 13 show that a larger advantage will be obtained by infusing into an artery which receives a small fraction of the cardiac output or by infusing a drug which has a low integral of recirculation because of drug loss due to rapid metabolism, rapid chemical change, irreversible tissue binding, or rapid excretion. A drug which persists for a prolonged time in the arterial blood will have large recirculation integrals and R_d will be close to 1.0 (no advantage). By assuming there is no loss of drug from the lungs, these relationships are illustrated in Fig. 3 for a cardiac output of 5.0 liters $\cdot$ min^{-1} and for varying values of α and ϕ (ϕ_a assumed equal to ϕ_v).

Another expression for R_d can be written in terms of the fraction (α) of cardiac output which flows through the infused artery, the probability (δ_s) that a drug molecule will be lost during a single passage through the systemic circulation, and the probability (δ_l) that drug will be lost during one passage through the lungs. This expression as derived in Appendix IV is

$$R_d = \frac{1 + [(1 - \alpha)/\alpha]\delta_s}{1 - \delta_l} \tag{14}$$

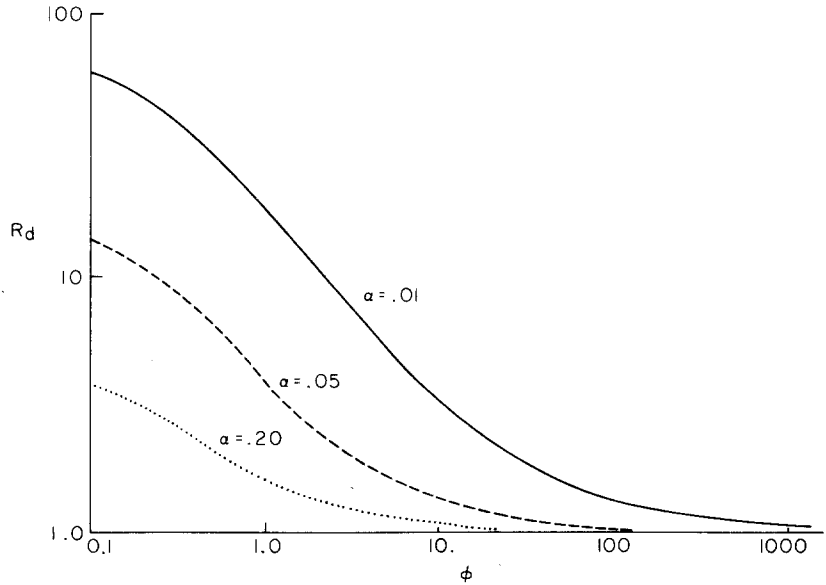

Fig. 3. Calculated relationship between the advantage of regional drug delivery (R_d) and the recirculation integral (ϕ) for various values of α (cardiac output is 5.0 liters $\cdot$ min^{-1}).

If there is no loss of drug in the lungs, then $\delta_1 = 0$ and

$$R_d = 1 + [(1 - \alpha)/\alpha]\delta_s \tag{15}$$

It is important to realize that δ_s includes all types of systemic drug loss (including that from the lungs) but that it does not include any drug loss within the region supplied by the infused artery. This agrees with the statement made earlier that parameters concerned with drug loss and distribution within this region do not influence R_d.

Several interesting observations can be made based on equations 14 and 15. For example, consider infusion into an artery which receives 10% of the cardiac output ($\alpha = 0.10$) of a drug which is lost only from one organ such as the kidney. If the rate of drug loss is equal to the rate of renal blood flow (assumed to be 20% of the cardiac output), then $\delta_s = 0.20/0.90$ (δ_s applies only to the portion of cardiac output which goes to the systemic circulation). Thus $R_d = 3.0$. In this case, it is possible to quickly estimate the advantage of arterial infusion into the site being considered without having to measure the integral of the recirculation function. This example also illustrates the small advantage which may be obtained despite relatively rapid clearance of a drug from the systemic circulation. However, if the same drug is considered for infusion into an arterial site with $\alpha = 0.01$, then $R_d = 21$.

EVALUATION OF FACTORS WHICH INFLUENCE THE ADVANTAGE OF DECREASED SYSTEMIC DRUG DELIVERY AFTER ARTERIAL INFUSION

In order to deliver less drug to the systemic circulation after arterial infusion, there must be loss of drug by metabolism, excretion, or chemical change during its first passage through the region being perfused by that arterial blood.

From the proof of Appendix III, it is obvious that the total drug delivered to any systemic region will be proportional to the amount of drug which reaches the heart for the first time. For the venous injection, this will represent the entire injection. If δ_b is defined as the probability that a molecule of drug will be lost from the body during a single passage through the region supplied by the infused artery, then for an arterial injection the amount reaching the heart for the first time will be equal to the total intra-arterial dose times $(1 - \delta_b)$. Thus equation 5 yields

$$R_d = (1 - \delta_b) \tag{16}$$

where now the smaller the value of R_d, the greater the systemic advantage.

In order to consider the factors which influence δ_b, $f_i(t)$ is defined as the fraction of the total injected dose which remains in the region perfused by the artery at any time (t) after infusion. This fraction includes only those molecules which have not left the region and therefore does not include any drug which has been delivered by recirculation. Assuming, for illustration, that there is a constant fractional rate of drug loss (σ_b) per unit time for the region, then

$$\delta_b = \sigma_b \int_0^\infty f_i(t)\, dt \tag{17}$$

The value of $\int_0^\infty f_i(t)\, dt$ is equal to the mean transit time ($\bar{t}$) for the drug in that region (10). Since $\bar{t}$ equals volume of distribution/blood flow, parameters which influence the effective volume of distribution of a compound such as capillary permeability and reversible binding along with tissue blood flow may be important in determining the systemic dose.

In contrast to the advantage of increased drug delivery to the target site, the advantage of decreased systemic drug delivery is dependent on the parameters of the target tissue. Thus the advantage of reduced systemic drug delivery after arterial infusion will be greatest when there is a large fractional rate of drug loss in the region supplied by the infused artery, when there is increased capillary permeability or tissue binding, and when there is a reduced rate of blood flow.

RELATIONSHIP BETWEEN DRUG DELIVERY AND PHARMACOLOGICAL ACTIVITY

In the discussions above, it was decided to evaluate the time integral of concentration at a particular site. Increased total drug effect at a particular site resulting from arterial infusion is dependent on the time integral of drug effect and not simply on the integral of concentration. Therefore, it is important to relate the quantitative statements above about drug delivery to the more complicated problem of drug activity.

It was demonstrated that the principles above apply in a linear system to the evaluation of the total time integral of drug concentration at any site within the region supplied by an infused artery. Therefore, these principles apply to the delivery of drug to the actual sites of pharmacological activity. In order to relate this delivery to activity, however, one must know the relationship between drug concentration in the active site at any time and the resulting effect.

For the purposes of this discussion, it is assumed that whenever drug is present at the active site it will exert some effect on a molecular level, even

though the activity may not be grossly measurable. Throughout this discussion, it is also assumed that the concentration–effect curve for a particular drug and particular tissue remains constant over time so that a given concentration will elicit a given effect at all times.

$E[C_b(t)]$ will be defined as the effect at any time t resulting from the presence of drug in the active site at concentration $C_b(t)$. In a manner analogous to that employed previously, the total pharmacological effect resulting from infusion of a given drug can be evaluated as follows:

$$\text{Total effect} = \int_0^\infty E[C_b(t)]\, dt \tag{18}$$

Defining R_e as the ratio of the total effect obtained by arterial infusion to that obtained by venous infusion, an expression similar to equation 6 can be written:

$$R_e = \left\{ \int_0^\infty E[C_b(t)]\, dt \right\}_{\text{arterial}} \Big/ \left\{ \int_0^\infty E[C_b(t)]\, dt \right\}_{\text{venous}} \tag{19}$$

It can be seen from equations 5 and 19 that R_e will equal R_d when the concentration–effect relationship can be described by a straight line passing through the origin. This condition is frequently satisfied when $C_b(t) \simeq 0$, for example, a slow infusion.

In order to relate R_e to R_d in general, we will first define $H[C_b(t)]$ as the effect per unit concentration:

$$H[C_b(t)] = E[C_b(t)]/C_b(t) \tag{20}$$

Thus

$$\text{Total effect} = \int_0^\infty H[C_b(t)]C_b(t)\, dt \tag{21}$$

If $H[C_b(t)]$ is constant, then substituting equation 21 into equation 19 and simplifying yields an expression identical to equation 5, which demonstrates that R_e is equal to R_d when the concentration–effect relationship is linear.

Difficulties are encountered in relating R_e to R_d when the slope of the concentration–effect curve is variable with concentration. For this, first consider a complex concentration–effect relationship, a biphasic curve which is first convex (gradually increasing change in effect per unit change in concentration) and then concave (gradually decreasing change in effect per unit change in concentration). This is illustrated by the sigmoid curve in Fig. 4. It is readily apparent that $H[C_b(t)]$ increases steadily from $C_b(t) = 0$ to $C_b(t) = C_m$ and then decreases as $C_b(t)$ continues to increase further. This is formally shown in Appendix V, where it is proven that a straight line

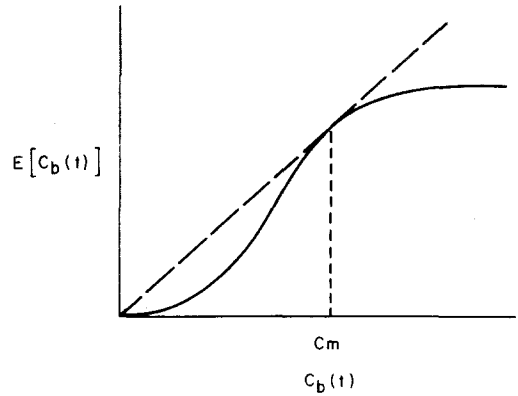

Fig. 4. Illustration of a biphasic sigmoid-shaped concentration–effect relationship.

drawn tangent to the curve and passing through the origin intersects the curve at a point, C_m, at which $H[C_b(t)]$ has either a maximum or a minimum value. It is also demonstrated in Appendix V that when the point of intersection, C_m, of the tangent line lies in a convex region of the curve, then $H[C_b(t)]$ will have a minimum value at that point; and when the point of intersection of the tangent line lies in a concave region of the curve, then $H[C_b(t)]$ will have a maximum value at that point.

For the concentration–effect relationship illustrated in Fig. 4, any increase in concentration between $C_b(t) = 0$ and $C_b(t) = C_m$ would result in an increase in effect greater than the increase in concentration, whereas any increase in concentration above $C_b(t) = C_m$ would result in a steadily diminishing effect per unit concentration. Any attempt to completely quantitate the advantage of increased pharmacological activity to be gained by arterial infusion for a drug with a biphasic concentration–effect relationship must allow for this variable change of the average effect per unit concentration, $H[C_b(t)]$, with concentration. One must either precisely measure the actual direct effect at each period of time or measure the concentration, $C_b(t)$, of drug at the active site at each time and know the relationship of $E[C_b(t)]$ to $C_b(t)$ over the whole concentration range encountered.

While it is not possible with present techniques to completely evaluate R_e, it is possible to evaluate certain limits of R_e based on determination of the magnitude of R_d. For drugs with biphasic concentration–effect curves, the relationship between R_d and R_e depends on the range of concentrations achieved by arterial and venous infusion. To do this, it is assumed that $C_b(t)$ after arterial infusion is greater than or equal to $C_b(t)$ after comparable venous infusion at all times following the start of infusion. This is likely to be true except in the unusual situation when the probability (δ_b) of drug loss

in the region supplied by the infused artery exceeds the probability of drug loss (δ_s) in the systemic circulation to a significant degree. Thus if $C_b(t)$ is less than C_m following infusion by both routes, then R_e will be greater than or equal to R_d. If $C_b(t)$ is approximately equal to C_m for a large part of the time that the drug is present after infusion by both routes, then R_e will be approximately equal to R_d. If $C_b(t)$ is greater than C_m for a large part of the time that the drug is present after infusion by both routes, then R_e will be less than or equal to R_d. These intuitive statements are formally proven in Appendix V. Similar approximations can be made for drugs with effects which are observable only at concentrations above a certain minimum level. Whereas it was decided to primarily evaluate direct effects of drug action, such that an effect can be considered to occur at every concentration, there is considerable interest in the evaluation of indirect effects of drug action. These evaluations are frequently complicated by the fact that minimum threshold concentrations are necessary before effects can be observed. This problem can be dealt with as an extreme case of the biphasic concentration–effect curve when one regards the slope of the initial convex portion of the curve to be very close to 0. Thus the general statements made above relating R_e to R_d for drugs with biphasic curves would also apply to the evaluation of drug effects in the presence of significant lower concentration thresholds.

It is also possible to evaluate the relationships between R_e and R_d for drugs whose concentration–effect curves are either completely convex or completely concave throughout the range of concentrations encountered. When discussing concave curves, only curves which approach an asymptote such that the slope is never decreasing will be considered. For a concave curve, with a steadily decreasing change in effect per unit concentration, $H[C_b(t)]$ will have a maximum value at the origin, whereas for a convex curve with a steadily increasing change in effect per unit concentration, $H[C_b(t)]$ will have a minimum value at the origin. The formal proof for these statements is again presented in Appendix V. It becomes apparent from equation 21 and these statements that R_e for a drug with a concave concentration–effect curve will be less than or equal to R_d, whereas for a drug with a convex concentration–effect curve R_e will be greater than or equal to R_d. The extent to which R_e approaches R_d will be highly dependent on the rate of drug infusion, since rapid rates of infusion will result in higher values of $C_b(t)$ for both arterial and venous infusions while slow infusions will result in low values for $C_b(t)$ by both routes. Rapid infusion rates lead to increasing deviation of the two values in both cases, with R_e becoming greater than R_d for drugs with convex curves and less than R_d for drugs with concave curves.

It was demonstrated previously that the magnitude of R_d is not dependent on the rate of drug infusion. This is also true for R_e when drug

effects are linearly proportional to the concentration C_b at the active site over the whole range of concentrations encountered. However, when the concentration–effect curve has a varying slope, the rate of infusion may play a very important role in determining the magnitude of R_e. For drugs with concave curves, slow infusions would provide maximum values for R_e (which would approach R_d as an upper limit), whereas for drugs with convex curves, rapid infusions would provide maximum values for R_e (which could be much larger than R_d). For drugs with biphasic curves, the maximum value for R_e would result from intermediate rates of infusion such that $C_b(t)$ from arterial infusion would be approximately equal to C_m for a large part of the time that drug is present in the body. This results because $H[C_b(t)]$ has a maximum value at concentration C_m. This discussion illustrates that knowledge of the mechanism of action of a drug and its concentration–effect relationship plays a critical role in choosing a rate of drug infusion for intra-arterial administration.

Knowledge of the concentration–effect relationship for a drug also determines the usefulness of determination of R_d for that particular drug. For drugs with convex curves over the range of concentrations involved, the value of R_d would simply set a lower limit for the advantage of increased drug effects, R_e, and a satisfactorily high value for R_d would justify a therapeutic trial of intra-arterial infusion. On the other hand, for drugs with concave curves R_d would serve as the upper limit for any advantage to be obtained by arterial infusion and therefore a low value would virtually exclude the usefulness of arterial infusion for drugs of this type. The usefulness of R_d for drugs which have a biphasic curve is somewhat more limited; however, useful approximations can be made as demonstrated above.

DISCUSSION

This paper represents an initial attempt to evaluate the factors which determine the advantages of administering drugs by intra-arterial infusion. With the understanding that no single model or treatment will be applicable for all drugs, some insight into the problem and its many complexities can be gained through the use of simplifying assumptions. It should be emphasized, however, that any application of the principles disclosed herein should be supported by a thorough understanding of the limitations of these assumptions.

The assumption that the rate coefficients of linear compartmental analysis remain constant would not be expected to be true in all cases because many circulatory parameters are undergoing constant change and because some drugs are distributed to parts of the body by other than

passive processes. As a necessary simplifying approximation, this assumption would seem to be reasonable, although one should guard against the potential errors which might result in some situations.

By choosing to evaluate drug delivery to regions which receive blood only from the infused artery, this analysis has been further simplified. It is readily seen in this case that values for R_d and R_e represent the maximal advantages which can be obtained by infusing into that artery. Any mixing of infused arterial blood with other sources of systemic arterial blood proximal to the site of interest would decrease the actual advantage obtained. If this mixing were large or highly variable, then R_d would serve mainly as a guideline for the exclusion of drugs for which there would be little expected benefit from arterial infusion.

For this evaluation, it was decided to evaluate total drug delivery and total drug effect by their respective time integrals and to use these integrals as criteria for the effectiveness of arterial infusions. The major justification for this approach comes from a realization that the advantages of arterial infusion cannot be completely evaluated at a single time. It was noted, from the literature, that considerable confusion has resulted from studies of tissue drug levels at selected times after intra-arterial and intravenous infusion. In addition, the most important clinical applications of arterial infusions involve drugs with which total activity over time is of major importance rather than activity at any single time period. It is important to realize, however, that when one is interested strictly in the ability of arterial infusions to provide a higher peak level of drug at a certain time, this analysis will offer little if any insight.

An important result of the use of the time integral of drug concentration is that it has permitted consideration of the advantages gained at the actual sites of pharmacological activity since it was shown that $\int_0^\infty C_b(t)\,dt$ is directly proportional to $\int_0^\infty C_0(t)\,dt$. This is of considerable practical benefit since it is far easier to measure the integral of the arterial concentration than it is to measure the actual levels of drug at the active sites within the tissue. In order to assess the advantages of arterial infusions more completely, it would be necessary to design experiments based on the direct measurement of pharmacological activity.

The decision to employ a particular arterial site for administration of a particular drug should be based on knowledge that an increased pharmacological effect will result compared to systemic administration. While R_e cannot be accurately determined with present techniques, an approach has been developed to allow approximations of R_e. These approximations are dependent on the assumptions above and are also dependent on the assumption that the concentration–effect relationship is constant with time. This may not be valid in certain situations where there is an increase or decrease

of available active sites, where there is irreversible damage to the region infused, or where there is repair, recovery, or some other change of the tissue involved in response to the presence of the drug. Nevertheless, when these assumptions are valid, approximations of R_e can be made based on measurement of the advantage of regional drug delivery, R_d, and a knowledge of the concentration–effect relationship over the range of concentrations encountered.

For drugs with linear concentration–effect curves and for other drugs whose concentrations are maintained at very low levels where their concentration–effect curves are linear, R_e will equal R_d. For drugs with convex curves R_e will be equal to or greater than R_d, and for those with concave curves R_e will be equal to or less than R_d. For drugs with biphasic concentration–effect curves, R_e may be greater than, equal to, or less than R_d depending on the concentration achieved. In assessing the advantage of increased regional pharmacological effects from arterial infusion, R_d would therefore be an accurate measurement for drugs with linear concentration–effect relationships, and would serve as a lower limit for drugs with convex concentration–effect curves and as an upper limit for those with concave curves.

In a recent review of the pharmacokinetics of drug action (11), it was shown that the concentration–effect curves for most drugs which have been evaluated were either linear or concave. This suggests that R_d will be useful for the assessment of R_e or its upper limit in many cases. Although accurate assessment of the relationship between R_e and R_d requires knowledge of the concentration–effect curve involved, R_d may serve as a first evaluation of the advantage of arterial infusion when such information is not available. However, while a significantly large value for R_d may provide justification for initial trials of arterial infusion, further conclusions must be carefully drawn when other important information about drug distribution and effect is not available.

Until it becomes possible to quantitatively evaluate the total pharmacological effects resulting from drug infusions, it is likely that measurement of the advantage of regional drug delivery, R_d, will serve as an important criterion in the choice of arterial administration. For this reason, it is important to understand the factors which determine the magnitude of R_d.

It was shown that the rate of local blood flow in the region being evaluated does not influence R_d, while the blood flow through the infused artery is very important because it determines the fraction, α, of cardiac output received by the artery. In Fig. 3, it was seen that infusion into an artery which receives 1% of the cardiac output will result in a significant R_d for any drug which has a recirculation integral less than 1000 times the infused dose. However, infusion into an artery which receives 20% of the

cardiac output would not result in a detectable advantage for a drug with a recirculation integral greater than 20 times the dose.

Under our assumptions, capillary permeability, tissue binding, and other parameters which determine exchange between capillary blood and the tissue under study do not influence R_d. These factors, however, are important in determining the absolute amounts of drug delivered and the relative value of one drug vs. another when given by intravenous infusion.

Once a particular artery has been chosen for infusion, the major factor influencing R_d is the time integral of the arterial level of recirculating drug. The ease with which this integral can be measured demonstrates that R_d may be easily determined for a wide variety of drugs. Whereas precise determination of R_d by equation 12 requires measurement of separate integrals of recirculation after arterial and venous bolus injections, R_d can be approximated in many cases by measuring the integral of recirculation after a venous bolus injection and assuming that ϕ_a equals ϕ_v. This determination would not be complicated by drugs with multiexponential decay curves since one simply would measure the time integral without concern for the shape of the curve. This simple approach would allow quick exclusion of many drugs which have large recirculation integrals such that no significant advantage could be expected from arterial infusion.

When employing arterial infusions, several factors may influence the choice of a particular rate of infusion. One of the most important of these is the concentration–effect relationship for the drug and tissue being evaluated. As demonstrated above, the shape of the concentration–effect curve determines which rate of infusion would lead to a maximal advantage of regional drug effects, R_e. For drugs with convex curves R_e would be maximal with rapid rates of infusion, whereas for drugs with concave curves R_e would be largest with slow rates of infusion. Drugs with biphasic curves require intermediate rates of infusion to achieve a maximal R_e. However, for drugs with linear concentration–effect relationships, the rate of infusion will have no influence on R_e. Other factors may be important in choosing a rate of infusion, such as the growth kinetics for infectious or malignant diseases, but these factors are not important in determining the advantages of arterial vs. venous infusion and therefore are not helpful in deciding between them.

It is important to realize that diminished systemic effects may result from arterial infusion as a result of decreased systemic drug delivery. It has been demonstrated how the rate of drug loss in the area supplied by the infused artery, the rate of tissue blood flow, and the various parameters which influence blood–tissue exchange are all involved in determining this advantage. However, practical application of this advantage requires that it be quantitated and exploited. In clinical situations where maximum system-

ically tolerated doses are used, as in cancer chemotherapy, higher total doses of certain drugs may be given by arterial infusion than by venous infusion. This advantage of reduced systemic drug delivery can be evaluated by comparing the respective integrals of systemic artery concentrations after intra-arterial and intravenous bolus injections.

In conclusion, the major goal of this paper is to offer insight into the complexities of accurately evaluating the advantages of arterial infusions of drugs. It is shown that the considerable advantage of increased drug delivery obtained during a single passage of the injected drug through the region supplied by the infused artery may be neutralized if the drug continues to recirculate in sufficient amount and for sufficient time. Infusion into an artery which receives a small fraction of the cardiac output is important, but cannot be considered sufficient justification for arterial infusion unless one knows the recirculation integral for the drug involved.

The choice of a rate of infusion and the relationship between R_e and R_d are dependent on the concentration–effect curve involved. Direct evaluation of R_e will require accurate measurement of the time integral of drug effects. These statements serve to emphasize that progress in the evaluation of arterial infusions will result from the measurement of drug effects and not simply from the measurement of drug concentrations in tissue at different times. Hopefully, realization of this will guide future experiments designed to evaluate the advantages of arterial infusions.

Until more definitive information is available about the direct measurement of drug effects and about concentration–effect curves for various drugs, measurement of the advantage of regional drug delivery, R_d, is offered as a means of obtaining a quantitative assessment of the value of arterial infusion for a particular arterial site and a particular drug. When the limitations of drawing conclusions from the value of R_d are understood, it is suggested that this value may be used as a first approximation to guide the practical application of arterial infusions.

APPENDIX I

The purpose of this appendix is to derive equation 4.

Consider the subsystem which includes all of the compartments which the drug can enter after passing through the artery being evaluated for infusion and from which the drug can reach the region under consideration without having to pass through this artery again. One of the major assumptions of this paper is that the region being considered can receive the drug only after it has passed through the infusional artery. This implies that this artery can be treated as an input point for the subsystem. For this subsystem, let $C_i(t)$ be the amount in the ith compartment and let $\mathbf{C}(t)$ be the

column vector of the C_is. Let k_{ij} be the rate constant from compartment j to compartment $i \neq o$, $j \neq i$; k_{oi} represent the rate constant for either loss of material from the ith compartment to the outside or chemical change of the material within the ith compartment; $k_{ii} = -[k_{oi} + \sum_j k_{ji}]$; and $\mathbf{K}$ be the matrix of the k_{ij}s (12). Further, let k_{io} be the rate constant for entrance of material into the ith compartment from the artery being evaluated for infusion and let $\mathbf{I}$ be the column vector of the k_{io}s. Finally, let $C_0(t)$ be the amount in this artery as a function of time. Hence the differential equation for this subsystem can be written as

$$\frac{d\mathbf{C}(t)}{dt} = \mathbf{K}\mathbf{C}(t) + \mathbf{I}C_0(t) \tag{A1}$$

Using the fact that at both $t = 0$ and $t = \infty$, $C_i(t) = 0$, and integrating both sides of equation A1 with respect to t from 0 to ∞, yields

$$0 = \mathbf{K}\int_0^\infty \mathbf{C}(t)\,dt + \mathbf{I}\int_0^\infty C_0(t)\,dt \tag{A2}$$

Rearranging equation A2 gives

$$\int_0^\infty \mathbf{C}(t)\,dt = (\mathbf{K}^{-1}\mathbf{I})\int_0^\infty C_0(t)\,dt \tag{A3}$$

Letting the ith element of the column vector be denoted by k_i', equation 4 then follows from equation A3. Q.E.D.

APPENDIX II

The purpose of this appendix is to show that for a linear system, whose parameters are time independent, R_d depends solely on the parameters of those regions which are not directly perfused by the artery into which the drug is infused and is independent of the parameters of the region under consideration.

Consider the system as a large, but finite, compartmental system with N compartments. Let $C_i(t)$ be the amount of material in the ith compartment at time t, and let $\mathbf{C}(t)$ be the column vector of the C_is. Let $\mathbf{K}$ be the matrix of the k_{ij}s as discussed in Appendix I. As will be proven in Appendix III, the arterial or venous injection may be treated, without any loss of generality, by assuming that $C_i(0)$ is 0 except for $i = a$ (for arterial injection) or $i = v$ (for venous injection) when $C_i(0)$ may be taken equal to 1. Thus the equation representing the time course of the distribution in the compartments may be written as

$$d\mathbf{C}/dt = \mathbf{K}\mathbf{C} \tag{A4}$$

Integrating both sides of the above equation from $t = 0$ to $t = \infty$, rearranging, and assuming that the material eventually disappears completely from the system yields

$$\int_0^\infty \mathbf{C}\, dt = -\mathbf{K}^{-1}\mathbf{C}(0) \tag{A5}$$

Let the elements of the inverse rate constant matrix, $\mathbf{K}^{-1}$, be denoted by κ_{ij}, and let the compartment which is being studied be denoted by the subscript b. Then, since

$$R_d = \left[\int_0^\infty C_b(t)\, dt\right]_a \Big/ \left[\int_0^\infty C_b(t)\, dt\right]_v \tag{A6}$$

the above definition along with equation A5 yields

$$R_d = \kappa_{ba}/\kappa_{bv} \tag{A7}$$

Since $\kappa_{ij} = (\text{cofactor } k_{ji})/(\det \mathbf{K})$, therefore

$$R_d = \text{cofactor}\,(k_{ab})/\text{cofactor}\,(k_{vb}) \tag{A8}$$

The connectivity of the system will now be made explicit. The artery into which the injection is made is assumed to be the unique pathway to the region b. The compartments may then be numbered in the following manner: For all $i > a$, a particle in compartment i has a pathway by which it can get to compartment b without passing through compartment a. Thus, for all $i < a$, a particle in compartment i can either not ever get to compartment b or, if it can get to compartment b, it *must* pass through a in the process. Therefore, under the above numbering rule, $a < b$, and under the assumption that a particle in compartment v must pass through compartment a in order to get to compartment b, $v < a$. Further, for all $i > a$ and $j < a$, $k_{ij} = 0$ since otherwise a particle in j could go directly to compartment i and then to compartment b without passing through compartment a, contrary to the assumptions for $j < a$. Thus $\mathbf{K}$ is a cut-reducible matrix, and therefore the ratio of the cofactors in equation A8 is dependent only on the terms of the matrix for which $i \leq a$ and $j < a$ (13). Hence R_d depends only on the parameters of the compartments which are not directly connected to compartment b but which can reach compartment b only by passing through compartment a, i.e., are independent of the parameters of the compartments which connect directly to compartment b without necessarily passing through compartment a. Q.E.D.

APPENDIX III

The purpose of this appendix is to show that for a linear system where parameters are time independent, the integral over all time of the amount

of a substance at any point within the system is dependent solely on the total amount of the substance which is injected into the system at some point and not on the time course of the injection.

Let $P(x, t_1, y, t_2)\, dt_2$ be the probability that a particle that enters the system at point x at time t_1 will be at point y at a time between t_2 and $(t_2 + dt_2)$. From the assumption that the parameters of the system are independent of time, this probability may be written as $P(x, y, t_3)\, dt_3$, where t_3 is equal to $(t_2 - t_1)$. Thus if $A(\tau)\, d\tau$ is the amount of material which is injected into the system at the point x during the time between τ and $(\tau + d\tau)$, the amount of material which is present at the point y at any time between t and $(t + dt)$ is therefore

$$\int_0^t A(\tau)P(x, y, t - \tau)\, d\tau\, dt$$

Hence the total amount of the substance which is present at the point y over all time is

$$\int_0^\infty \int_0^t A(\tau)P(x, y, t - \tau)\, d\tau\, dt$$

Interchanging the order of integration and substituting z for $(t - \tau)$ transforms the previous integral to

$$\int_0^\infty \int_0^\infty A(\tau)P(x, y, z)\, dz\, d\tau$$

which may be rewritten as

$$\int_0^\infty A(\tau)\, d\tau \int_0^\infty P(x, y, z)\, dz$$

Since $\int_0^\infty A(\tau)\, d\tau$ is the total amount of the substance that is injected, Q.E.D.

APPENDIX IV

The purpose of this appendix is to derive equation 14. The notation of the paper will be used plus an additional term δ_b'. The term δ_b' denotes the probability that a molecule which is in the infused artery will be permanently removed from the system—including the possible loss of the molecule in the lungs—before it reaches the aorta. The assumptions involved are the same as those listed in the text and the previous appendices plus the assumption that for a venous injection the drug will travel directly to the heart and not suffer any loss before it reaches the heart for the first time.

It will be useful to first derive a preliminary formula. Of the number of molecules, G, present in the aorta at a given time, a certain fraction will be

at the aorta one passage later. Since the fraction of the molecules at the aorta that go to the artery is α and the fraction of those that are then removed from the system before reaching the aorta again is δ_b', the number of molecules removed in the first pass by this route will be $G\alpha\delta_b'$. Similarly, since the fraction of the molecules that go to the rest of the body is $(1 - \alpha)$, and the fraction of those that are removed from the system before reaching the aorta again is δ_s, the number of molecules removed in the first pass by this route will be $G(1 - \alpha)\delta_s$. Thus the number of molecules that return to the aorta after one passage will be given by $[G - G\alpha\delta_b' - G(1 - \alpha)\delta_s]$, which may be rewritten as

$$G\{1 - [\alpha\delta_b' + (1 - \alpha)\delta_s]\} \tag{A9}$$

By induction, the number of molecules that are present at the aorta after n passages will be given by

$$G\{1 - [\delta_b' + (1 - \alpha)\delta_s]\}^n \tag{A10}$$

Now consider the arterial injection. Based on the results of Appendix III, the injection may be taken simply as a bolus of material of number N_0. Of this number, the amount that reaches the aorta without being permanently removed will be $N_0(1 - \delta_b')$. If this is equated to G above, the number that are at the aorta after each passage may be easily calculated by means of formula A10 above. Since the number of molecules at the artery after each passage is simply α times the number at the aorta, the total number of molecules that are at the artery over all time is then given by

$$\begin{aligned}\left[\int_0^\infty C_0(t)\,dt\right]_{\text{arterial}} &= N_0 + \alpha N_0(1 - \delta_b') \\ &+ \alpha N_0(1 - \delta_b')\{1 - [\alpha\delta_b' + (1 - \alpha)\delta_s]\} \\ &+ \alpha N_0(1 - \delta_b')\{1 - [\alpha\delta_b' + (1 - \alpha)\delta_s]\}^2 + \cdots\end{aligned} \tag{A11}$$

The series may be summed, and the summation, after elementary rearrangement, yields

$$\left[\int_0^\infty C_0(t)\,dt\right]_{\text{arterial}} = N_0\left\{\frac{\alpha + (1 - \alpha)\delta_s}{\alpha\delta_b' + (1 - \alpha)\delta_s}\right\} \tag{A12}$$

Consider now the venous injection. The number of molecules injected will be equal to N_0 as with the arterial injection. Thus the number of these molecules that reach the aorta without being permanently removed will be equal to $N_0(1 - \delta_l)$. By a completely analogous argument to that used for the arterial injection, the total number of molecules that are at the artery

will then be given by

$$\left[\int_0^\infty C_0(t)\,dt\right]_{\text{venous}} = \alpha N_0(1-\delta_l) + \alpha N_0(1-\delta_l)\{1-[\alpha\delta_b' + (1-\alpha)\delta_s]\}$$
$$+ \alpha N_0(1-\delta_l)\{1-[\alpha\delta_b' + (1-\alpha)\delta_s]\}^2 + \cdots$$

This series may be summed to yield

$$\left[\int_0^\infty C_0(t)\,dt\right]_{\text{venous}} = N_0\left\{\frac{\alpha(1-\delta_l)}{\alpha\delta_b' + (1-\alpha)\delta_s}\right\} \tag{A13}$$

Thus substituting equation A12 and A13 into equation 6 and rearranging yields equation 14. Q.E.D.

APPENDIX V

The purpose of this appendix is to validate the various assertions involving $H[C_b(t)]$ made in the text.

a. If a straight line can be drawn from the origin tangent to the curve of $E[C_b(t)]$ vs. $C_b(t)$ (see Fig. 4), the point of tangency is an extremum of $H[C_b(t)]$ (i.e., a maximum or a minimum value of $H[C_b(t)]$).

Proof:

Let the point of tangency be denoted as $\{C_\tau(t),\ E[C_\tau(t)]\}$. Since the tangent line passes through the origin and the slope of the curve of $E[C_b(t)]$ vs. $C_b(t)$ at the point of tangency equals the slope of the tangent line, then

$$\frac{dE[C_\tau(t)]}{dC_\tau(t)} = \frac{E[C_\tau(t)]}{C_\tau(t)} \tag{A14}$$

At a value of $C_b(t) = C_m(t)$ for which $H[C_b(t)]$ is an extremum,

$$\frac{dH[C_m(t)]}{dC_m(t)} = 0 \tag{A15}$$

Inserting equation 20 into equation A15 and simplifying yields

$$\frac{dE[C_m(t)]}{dC_m} = \frac{E[C_m(t)]}{C_m(t)} \tag{A16}$$

Since equation A15 satisfies the requirements of equation A16, Q.E.D.

b. If $H[C_m(t)]$ is an extremum, a straight line from the origin can be drawn tangent to the curve of $E[C_b(t)]$ vs. $C_b(t)$ at this point.

Proof:

Since $H[C_m(t)]$ is an extremum, equation A16 is valid by an argument analogous to that used in the proof above. Since the tangent to the curve at the point $C_m(t)$ has the slope given by equation A16, and passes through the point $\{C_m(t), E[C_m(t)]\}$, it will pass through the origin. Q.E.D.

c. If $H[C_b(t)]$ has an extremum in a region of $C_b(t)$ for which the curve for $E[C_b(t)]$ is concave, then the extremum is a maximum, whereas if the curve is convex, then the extremum is a minimum.

Proof:

Inserting equation A16 into the second derivative of equation 20 with respect to $C_b(t)$ at an extremum point and rearranging yields

$$\frac{d^2H[C_m(t)]}{dC_m^2(t)} = \frac{1}{C_m(t)} \frac{d^2E[C_m(t)]}{dC_m^2(t)} \tag{A17}$$

Since $C_m(t) > 0$, the sign of $d^2H[C_m(t)]/dC_m^2(t)$ is the same as the sign of $d^2E[C_m(t)]/dC_m^2(t)$, which is positive for a convex curve and negative for a concave curve. Q.E.D.

d. In any range of $C_b(t)$ for which $E[C_b(t)]$ is always concave or always convex, there is at most one extremum of $H[C_b(t)]$.

Proof:

From the previous proof, in any region of $C_b(t)$ for which $E[C_b(t)]$ is always concave or always convex, if there is more than one extremum of $H[C_b(t)]$ they will all be maximums or all be minimums, respectively. But since $E[C_b(t)]$ is assumed to be well behaved, there must be a minimum between two maximums or *vice versa*. Q.E.D.

e. At the origin, $H[C_b(t)]$ has an extremum which is either a maximum if $E[C_b(t)]$ is concave there or a minimum if $E[C_b(t)]$ is convex there. Furthermore, this is the only extremum in the region about the origin for which the curve for $E[C_b(t)]$ is always concave or always convex.

Proof:

Consider the function

$$W[C_b(t)] = C_b(t)\frac{dE[C_b(t)]}{dC_b(t)} - E[C_b(t)] \tag{A18}$$

defined in the region of $C_b(t)$ about the origin for which the curve for $E[C_b(t)]$ is always concave or always convex.

Differentiating equation A18 with respect to $C_b(t)$ yields

$$\frac{dW[C_b(t)]}{dC_b(t)} = C_b(t)\frac{d^2E[C_b(t)]}{dC_b^2(t)} \tag{A19}$$

Since $C_b(t) > 0$, $dW[C_b(t)]/dC_b(t)$ has the same sign as $d^2E[C_b(t)]/dC_b^2(t)$. From equation A18, $W(0) = 0$ since $E(0) = 0$. Thus $W[C_b(t)]$ has the same sign as $d^2E[C_b(t)]/dC_b^2(t)$.

If equation 20 is differentiated with respect to $C_b(t)$ and inserted into equation A19, then

$$\frac{dH[C_b(t)]}{dC_b(t)} = \frac{W[C_b(t)]}{C_b^2(t)} \tag{A20}$$

Thus $dH[C_b(t)]/dC_b(t)$ has the same sign as $d^2E[C_b(t)]/dC_b^2(t)$. If the curve for $E[C_b(t)]$ is convex, $d^2E[C_b(t)]/dC_b^2(t)$ is positive. As a result,

$$dH[C_b(t)]/dC_b(t)$$

is positive and thus $H(0)$ is a minimum in this region. A similar argument for the concave region applies. Furthermore, since $dH[C_b(t)]/dC_b(t)$ does not change sign in this region, there is only one extremum value. Q.E.D.

f. If $H[C_m(t)]$ is a maximum, then for a given total amount of drug, the total effect is maximum when $C_b(t) = C_m(t)$.

Proof:

Since $H[C_m(t)] > H[C_b(t)]$, therefore equation 21 yields

$$\text{Total effect} = \int_0^\infty H[C_b(t)]\, C_b(t)\, dt \leq \int_0^\infty H[C_m(t)]\, C_b(t)\, dt$$

$$= H[C_m(t)] \int_0^\infty C_b(t)\, dt$$

$$= H[C_m(t)] \cdot (\text{total amount of drug}) \quad \text{Q.E.D.}$$

GLOSSARY

1. b, Subscript which relates to the site of pharmacological activity.
2. C_i, Amount of drug in any compartment (i).
3. $\int_0^\infty C_i\, dt$, Time integral of amount of drug in any site (i) during the whole time that drug is present in the body. This represents the total delivery of drug to that site.

4. $C_0(t)$, Time-dependent function describing the amount of drug in arterial blood upstream from the site where arterial infusion is being evaluated.
5. C.O., Cardiac output (liters $\cdot$ min^{-1}).
6. $E[C_b(t)]$, Pharmacological effect at any time (t) resulting from the presence of drug in the active site in amount C_b.
7. F, Rate of blood flow through the artery which is being evaluated for arterial infusion (liters $\cdot$ min^{-1}).
8. $f_i(t)$, Probability that a drug molecule will remain in the region supplied by the infused artery at any time (t) during the first passage through the region after arterial infusion.
9. $H[C_b(t)]$, Pharmacological effect per unit amount of drug.
10. I_a, Time integral of arterial concentration during the first passage of drug through the artery after arterial infusion.
11. $I_{ra,rv}$, Time integrals of arterial drug concentration during recirculation of drug after arterial and venous infusion, respectively (recirculation integrals).
12. I_v, Time integrals of arterial concentration during the first passage of drug through the arterial circulation after venous infusion.
13. k_1, Rate coefficient corresponding to the rate of tissue blood flow (min^{-1}).
14. k_2, Rate coefficient representing the reciprocal of mean capillary transit time (min^{-1}).
15. $k_{3,4}$, Rate coefficients which govern blood–tissue exchange (min^{-1}).
16. k_i', Rate coefficient resulting from combination of several rate coefficients for the ith region (min^{-1}).
17. N_A, Avogadro's number.
18. N_i, Total number of drug molecules infused.
19. N_0, Number of drug molecules which enter the artery being evaluated for the first time after infusion.
20. N_t, Total number of drug molecules which enter the artery being evaluated for arterial infusion during the time that drug remains in the body.
21. R_d, Ratio of drug delivery ($\int_0^\infty C_i\,dt$) to any site (i) by arterial infusion compared to venous infusion.
22. R_e, Ratio of the total pharmacological effects, $\int_0^\infty E[C_b(t)]\,dt$, after arterial infusion to those after venous infusion.
23. $\bar{t}$, Mean transit time.
24. α, Fraction of cardiac output which flows to the artery being evaluated for infusion.
25. β, Probability that a drug molecule will enter the artery being evaluated for arterial infusion at least one time after that molecule has been administered by venous infusion.

26. δ_b, Probability that a molecule of drug will be lost from the body during a single passage through the region supplied by the infused artery.
27. δ_l, Probability that a molecule of drug will be lost from the body during a single passage through the lungs.
28. δ_s, Probability that a molecule of drug will be lost from the body during a single passage through the systemic circulation, excluding the region supplied by the infused artery.
29. θ, Average number of times that any molecule appears in the artery being considered.
30. σ_b, Probability per unit time that a molecule of drug which is present in the region supplied by the infused artery will be lost from the body.
31. $\phi_{a,v}$, Recirculation integral per unit total dose per liter after arterial and venous infusion, respectively (min · liter^{-1}).

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