Scaling Laws for Plasma Concentrations and Tolerable Doses of Anticancer Drugs

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Abstract

General scaling laws are developed for projecting measurements of the plasma concentrations of anticancer drugs from laboratory animals to humans and among humans of different sizes. Associated scaling laws for critical drug doses are established from these laws. Broad categories of single and periodic i.v. bolus dosings are considered. Validity of the relations is shown using measurement from the literature for several well-known cytotoxic agents. The scaling theory is also shown to apply to novel anticancer drugs now available or presently under development, as represented by the p.o. administered prodrug capecitabine, the gene silencing inhibitor zebularine, and the blood vessel inhibitor bevacizumab. Scaling considerations for the modern practice of combination chemotherapy are also discussed.

Introduction

Because of critical dosing requirements in cancer chemotherapy, it is general practice to express recommended doses of anticancer drugs in terms of body surface area rather than body mass so that presumably safe, yet effective, doses for individuals can be determined more precisely than otherwise. Involved here is not only dosage determination in clinical practice but also the scaling of tolerable doses from laboratory animals to humans for guidance with starting doses in clinical trials. The physical basis for this dosing practice rests in the plausible assumption that drugs are used and expended in the body by basic physiologic processes that vary with body surface area rather than body weight (1). Although various studies (1, 2) have provided a general endorsement for this concept, measurements of critical doses of laboratory animals and humans, when referenced to their body surface areas, have often differed appreciably from one another, contrary to the equal values expected. For example, for the well-known agent 5-fluorouracil (5-FU) and a schedule of 1 dose per day for 5 days, Freireich and colleagues (2) reported measured maximum tolerable doses for the monkey and human of about 210 and 500 mg/m², respectively. These and other measurements thus indicate that the matter of scaling of drug doses from laboratory animals to humans and among humans of different sizes is not yet a settled matter and that the subject can benefit from further study.

In earlier work, the author (3, 4) applied physiologic theory for fluid transfer across capillary walls to develop a connection between the time history of concentrations of the anticancer agent methotrexate in the blood of mouse and human. Recent further work on this subject has, in fact, now revealed a more general scaling theory for concentration-time measurements as well as related scaling laws for drug dosage that ensure similar systemic exposure for both single and periodically administered agents. The purpose of the present article is to discuss these new developments.

Materials and Methods

Materials used in this work are mainly measurements of the time history of plasma concentrations and critical doses of various anticancer agents, as reported in the literature. The overall method of the present work involves (a) development and confirmation of a general algebraic relation describing plasma concentrations of anticancer agents, and (b) application of this relation in establishing scaling laws for projecting critical doses of these agents from small mammals to humans and among humans of different sizes.

Results

Scaling theory for plasma concentrations

The algebraic description of the time history of drug concentrations in the blood is developed here in a relatively general form that is independent of many of the details of the contributing processes. In particular, a drug of initial mass \( M_0 \) is first assumed to be injected fully into an element of blood as it passes the injection site. Following injection, a basic process is envisioned where exchange of water and drug with surroundings occurs as the element passes through the capillary system and where, after the first few rounds of circulation, the entire amount of drug initially in the element has been removed and some of it returned, with a tendency toward uniform distribution in the blood.
The time for the process will of course equal the product of the time for a complete cycle of circulation, say $T$, and the number of cycles, say $N$, needed before this condition is reached.

The mass of drug $\Delta M_D$ returned after the initial number of cycles of blood circulation can be considered to be proportional to the net volume of the mixture of water and drug that is reabsorbed into the plasma over the time $NT$. The latter is described by the product of this time and the net inflow $Q$ of the mixture. The actual drug mass $\Delta M_D$ reabsorbed must then equal this product $QNT$ when multiplied by the average drug mass per unit volume of the mixture, and this, in turn, can be expected to be proportional to the initial drug mass $M_D$ per unit volume of plasma $V_p$. On dividing $\Delta M_D$ and $QNT$ by the plasma volume, the governing proportional relation (with symbol $\propto$ denoting proportionality) may thus be written as

$$\frac{\Delta M_D}{V_p} \propto \frac{M_D}{V_p} \frac{QNT}{V_p} \quad (A)$$

During this early stage, plasma protein binding with the drug can occur and effectively remove some of the drug from further action. This can be accounted for by including a factor $U$ on the right side of this relation (Eq. A) that denotes the fraction of unbound drug left after the binding process. In addition, plasma volume may be replaced by body mass $M$ on the right-hand side of this proportional relation, consistent with known variation among mammals of different sizes (5). Physiologic scaling theory developed in earlier work by the author (3–7) further requires that the flow $Q$ across capillary walls must scale with body mass to the power $5/6$ and that the time for circulation $T$ must scale as body mass to the $1/4$th power. The product $Q'T$ must therefore vary with $M$ to the $13/12$th power.

With additional cycles of circulation, a reduction of drug in the blood will occur as a result of additional transfer processes in the capillaries. This continuing decrease in the concentration can be described in terms of times to a factor $f(t/NT)$, where $f(\cdot)$ denotes a function of the dimensionless time $t/NT$ (denoting the number of groups of $N$ cycles that have occurred up to time $t$). The concentration of drug $C$ (in units of drug mass per unit volume of plasma) may thus be expressed as

$$C = \frac{D}{M} \frac{UQNT}{M} f\left(\frac{t}{NT}\right) \quad (B)$$

where $D$ denotes the initial drug mass per unit of body mass.

Now, if the ratio $t/NT$ is fixed in this relation (Eq. B), the value of the function $f(\cdot)$ will also be fixed and the ratio on the left-hand side of this relation must then be proportional to the first ratio on the right. This provides the scaling law for the normalized concentration $C/D$ as a function of time. Thus, the ratio $C/D$ when multiplied by the ratio $M/UQNT$ must equal the constant proportionality factor implied by Eq. B. Using the above-noted dependence of the product $Q'T$ on body mass, the scaling law for the relative concentration may accordingly be written for human (subscript $H$) and laboratory animal (subscript $M$) as

$$\left(\frac{C}{D}\right)_H \frac{M^{1/12}_H}{U^{1/12}_H N^{1/12}_H} \propto \left(\frac{C}{D}\right)_M \frac{M^{1/12}_M}{U^{1/12}_M N^{1/12}_M} \quad (C)$$

together with the condition that the ratio $t/NT$ is the same for human and laboratory animal.

For the case of “complex drug behavior,” where one or both of the factors $U$ and $N$ are different for the human and laboratory animal, the scaling relations may be written from Eq. C as

$$\left(\frac{C}{D}\right)_H = \frac{U^1_H}{U^{1/12}_M N^{1/12}_M} \left(\frac{M^{1/12}_H}{M^{1/12}_M}\right) \left(\frac{C}{D}\right)_M \quad (D)$$

$$t_H = \frac{N^1_H}{N^{1/12}_M} \left(\frac{M^{1/12}_H}{M^{1/12}_M}\right)^{1/4} t_M \quad (E)$$

Because variables associated with time aspects of concentration measurements from laboratory animals can usually be represented by so-called allometric relations involving body mass raised to a fixed power (8), it can be expected from Eq. E that the ratio of circulation factors can similarly be so represented. This is indeed the case, as will be seen below.

The validity of Eqs. D and E is illustrated in Fig. 1 for concentration data (mg/L per mg/kg) reported by Mitsuhashi and colleagues (9) for an i.v. bolus injection of the anticancer agent nimustine hydrochloride. Here, adjustment was made for measured total (rather than unbound) concentrations.

![Figure 1](image-url) Measured concentration data from the mouse and dog scaled to the human with Eqs. D and E and compared with actual measurements. Basic data source: ref. 9.
Calculations provided values of $U_H/U_M$ for human and mouse (1.6) and human and dog (2.5), and the concentration data indicated that $N_H/N_M$ must vary with $M_H/M_M$ to the power $-0.10$.

**Pharmacokinetic variables.** Directly connected with the scaling of concentration data are the associated scaling laws for various pharmacokinetic variables. These follow from the above work and may be tabulated for human and laboratory animal as follows: all particular time variables $T^*$ such as half-life and mean residence time must scale as

$$T^* = \left( \frac{N_H}{N_M} \right)^{1/4} T_M^{*}$$

the clearance $Cl$ as

$$Cl^* = \left( \frac{N_M}{N_H} \right)^{2/3} \left( \frac{M_H}{M_M} \right)^{2/3} Cl_M$$

and volumes $V$ as

$$V^* = \left( \frac{N_M}{N_H} \right)^{11/12} V_M$$

For the case of "simple drug behavior" (factors $U$ and $N$ same for laboratory animal and human), it can be seen that times $T^*$, clearance $Cl$, and volumes $V$ must scale with body mass to powers of $1/4$th, $2/3$rd, and $11/12$th, respectively.

**Scaling theory for single i.v. bolus doses**

Significant results associated with scaling laws for drug dosage follow from the above general description of plasma concentrations. Attention is restricted first to single i.v. bolus doses. The similarity condition for drug dosing is assumed to be as follows: that the plasma concentrations $C$ for the human and laboratory animal (or another human) must be the same at corresponding times $t/NT$.

The requirement for this "similar-exposure" condition follows from Eq. B such that

$$D_H/U_H N_H^{1/12} = D_M U_M N_M M_M^{1/12}$$

The general form of this equation provides the scaling equation for drug dosage in the form

$$\left( \frac{M_D}{S} \right)_H = \left( \frac{U_M}{U_H} \right) \left( \frac{N_H}{N_M} \right) \left( \frac{M_H}{M_M} \right)^{1/4} \left( \frac{M_D}{S} \right)_M$$

where the drug mass $M_D (=D \times M)$ has been referenced to body surface area $S$, with the latter assumed proportional to body mass to the $2/3$rd power and with the proportional coefficient equal to 0.10 m$^2$/kg when needed, for example, for unit conversion (5).

For illustration of applicability of Eq. J, attention may be directed to critical doses of drugs from the platinum anticancer agents, as reported by Clark and colleagues (10). Single i.v. bolus doses were used in the study. Measurements for the dog and human (with assumed body masses of 8 and 70 kg, respectively) are found here to follow well the predictions from Eq. J for the case of simple drug behavior ($U_M = U_H$ and $N_M = N_H$). Results are shown in Fig. 2 where measurements of the critical (maximum tolerated) dose for humans are compared with predictions from measurements on dogs when determined only from body surface area (no scaling) and, alternatively, from Eq. J. The latter clearly shows superior agreement with the measurements.

**Scaling theory for periodic i.v. bolus doses**

Attention is next directed to periodically administered i.v. doses, with the rate of drug dose $D^p$ defined as $\Delta D/\Delta t$, where $\Delta t$ denotes the interval between injections of amount $\Delta D$ (per unit of body mass, as earlier). In the usual way, $\Delta t$ and the total number of injections, say $n$, then define the schedule for dosing. The scaling law for rate of drug dose in the human in terms of that for the laboratory animal can be determined from the basic relation of Eq. B when $D$ is replaced by $D^p/\Delta t$ and the function $f$ is expanded to include the ratio $\Delta t/NT$ and the number $n$ of doses given, that is,

$$\frac{C}{D^p} \propto \frac{U_H}{N_H} \left( \frac{M_H}{M_M} \right)^{1/2} \left( \frac{M_D}{S} \right)_M \left( \frac{t}{NT} \frac{\Delta t}{NT} \right)^n$$

Now, the similarity condition here for periodic drug dosing among humans and laboratory animals is assumed to be an expanded version of that for single dosing, namely, that the plasma concentrations $C$ of the human and laboratory animal (or another human) must be the same at corresponding times $t/NT$ when the ratio $\Delta t/NT$ and the number of doses $n$ are fixed.

Requirements for this similar-exposure condition within the framework of the present theory can be determined in...
a manner like that used earlier in obtaining the relation of Eq. J. The general scaling equations for critical dose rate $M_D^R$ per unit of body surface area $S$ are expressible as

$$\left(\frac{M_D^R}{S}\right)_H = \frac{U_M}{U_H} \left(\frac{N_M}{N_H}\right)^2 \left(\frac{M_D^R}{S}\right)_M \quad (L)$$

with

$$\Delta t_M = \left(\frac{N_M}{N_H}\right)^{1/4} \Delta t_H \quad (M)$$

An interesting result from Eqs. L and M arises for the case of simple drug behavior ($U_M = U_H$ and $N_M = N_H$), where Eq. L reduces to the condition that the rate of drug dose per unit of body surface area is the same for human and laboratory animal. This is a noteworthy result because it is based on fundamental physiologic processes and yet provides a basis for scaling of drug dosage with body surface area, such as that discussed in the introductory remarks. Of course, it is now seen from Eq. M (with $N_H = N_M$) that a restriction on drug schedules accompanies this scaling law such that the time interval between injections must scale with body mass to the 1/4th power and, with a fixed total number of injections, that the total period for injections must similarly scale in this manner. That scaling of drug schedules should accompany scaling of critical doses from laboratory animals to humans was recognized and discussed earlier by Mordenti (11).

Approximate formula. For an approximate adjustment of the theory to account for a fixed schedule for both humans and larger laboratory animals such as dogs and monkeys, the strict requirement of precise similarity of concentration-time histories for human and laboratory animal may be relaxed, and the average value of the ratios $\Delta t/\Delta t_T$ for the two may be assumed in the function $f$ of Eq. K. In this case, drug dosage is based on similarity of an average concentration-time history, and Eq. K then requires (with $r$ constant and $\Delta t_M = \Delta t_H = \Delta t$) the single scaling relation

$$\left(\frac{M_D^R}{S}\right)_H = \frac{U_H}{U_M} \frac{N_H}{N_M} \left(\frac{M_H}{M_M}\right)^{1/4} \left(\frac{M_D^R}{S}\right)_M \quad (N)$$

This approximate equation for periodic rate of dosing is similar to the exact relation of Eq. J for single i.v. bolus doses and becomes identical to it when both sides of Eq. N are multiplied by the common interval $\Delta t$.

For illustration of the adequacy of Eq. N for periodic dosing with fixed schedule, attention may be directed back to the introductory remarks on studies of 5-FU with a dosing schedule of 1 dose per day for 5 days. The maximum tolerated doses for the monkey and human were noted to be approximately 210 and 500 mg/m² per day, respectively. Using Eq. N, with the assumption of simple drug behavior ($U_M = U_H$ and $N_M = N_H$), the dose for the monkey ($M_M = 3$ kg) when scaled to the human ($M_H = 70$ kg) is found equal to 460 mg/m² per day and, thus, is consistent with the measurements (within 8% or so).

Figure 3. Measurement of time history of plasma concentrations in monkeys for p.o. administration of capecitabine and corresponding scaled values from the mouse using Eqs. D and E. Basic data source: ref. 12.

Applications of theory

It is of interest to apply the scaling theory of the present work to measurements from some relatively new agents for cancer chemotherapy, as represented here by the now available antitumor agents capecitabine and bevacizumab and by the experimental antitumor drug zebularine, presently under development. Such applications are discussed below. In addition, scaling theory and application are discussed for the modern practice of combination chemotherapy.

(a) P.o. administered drugs: capecitabine. Work here has thus far been concerned with scaling laws for i.v. bolus administration of anticancer agents. In contrast, results are presented here for capecitabine, an agent that allows p.o. administration and also has novel antitumor activity because of its ability to change from a relatively inactive substance, as administered, to the antitumor agent 5-FU (discussed above) at the tumor site.

Onodera and colleagues (12) have provided measurements of the plasma concentrations of capecitabine after single p.o. administrations to monkeys and mice. These data may be examined using the scaling laws of Eqs. D and E, with subscripts MK (monkey) and MS (mouse) momentarily replacing H and M. Assuming typical values of body mass of the monkey $M_{MK}$ and mouse $M_{MS}$ of 3 and 0.02 kg, respectively, inspection of the data shows that these equations will apply when the nonbinding fractions $U_{MK}$ and $U_{MS}$ are equal and when the ratio $N_{MK}/N_{MS}$ is equal to the ratio $M_{MK}/M_{MS}$ raised to the power 0.08. Results from this scaling are shown in Fig. 3 using measurements from the mouse with a dose of 539 mg/kg and from the monkey with doses as indicated. The agreement can be seen to be good.
The approximate relation for scaling dose rate from monkey to human with fixed dosing schedule follows from Eq. N on assuming descriptions for nonbinding fractions and circulation numbers like that described above. Evidence that it is applicable can be found in the work of Cassidy and colleagues (13) and Budman and colleagues (14) for twice-daily dosing of monkeys and humans over an extended period of 4 to 6 weeks. Here, the highest nontoxic dose rate for the monkey ($M_M = 3$ kg) was observed to be approximately $520$ mg/m$^2$ per day. Equation N accordingly provides the scaled value for the human ($M_H = 70$ kg) of $1,470$ mg/m$^2$ per day, and this compares favorably with the measured value of $1,330$ mg/m$^2$ per day for the human.

(b) Gene silencing inhibitor: zebularine. The experimental agent zebularine is a small-molecule inhibitor that acts to limit the cancer-induced silencing of tumor suppressor genes. Holleran and colleagues (15) have reported measurements of the time history of plasma concentrations of zebularine for mice and monkeys following i.v. bolus injection, and it is worthwhile to examine these measurements in terms of the present work. Again, it is convenient to momentarily let subscripts MK (monkey) and MS (mouse) replace H and M in Eqs. D and E. Inspection of the data suggests that $U_{MK} = U_{MS}$ and that the ratio $N_{MK}/N_{MS}$ must vary with the ratio $M_{MK}/M_{MS}$ raised to the power $-0.05$. Figure 4 shows application of the scaling equations D and E when data from the mouse (with body mass $M_{MS} = 0.02$ kg) for single i.v. bolus dose of $100$ mg/kg are scaled to the monkey (with body mass $M_{MK} = 7$ kg) and compared with direct measurements for a dose of $500$ mg/kg. It can be seen that the scaled and measured values agree well with one another.

Regarding effective and tolerable dosings of zebularine, Cheng and colleagues (16) have shown that daily p.o. administration of $2,720$ mg/m$^2$ of this drug to tumor-bearing mice is associated with a decrease in tumor volume of about $20\%$ over an 18-day treatment period, in contrast with about a $250\%$ increase for similar untreated mice. In the work referred to above, Holleran and colleagues have further shown that the percentage of p.o. administered zebularine that finds its way to the blood is only about $7\%$, so that a safe yet effective daily i.v. dose for the mouse can be expected to be $190$ mg/m$^2$ per day for some 18 days.

For comparison purposes, this effective i.v. dose and schedule can be scaled to that for the human using exact scaling theory as represented by Eqs. L and M. Results are as follows: dose rate $= 430$ mg/m$^2$ per day with interval of $5.11$ days and total dosing period of $18 \times 5.11 = 92$ days. The actual dose per interval is of course $5.11 \times 430 = 2,200$ mg/m$^2$, and consistent with the dosing of the mice, this dose is to be administered at the beginning of each of the 18 intervals.

(c) Blood vessel inhibitor: bevacizumab. The relatively new agent bevacizumab is an anticancer drug that acts to block the growth of new blood vessels needed for tumor growth. In a preclinical study of its pharmacokinetics, Lin and colleagues (17) have determined time histories of its plasma concentrations for mouse and monkey, and Gordon and colleagues (18) have given clinical data for humans. These measurements can be compared with predictions from Eqs. D and E. Inspection indicates a characterization similar to that just discussed for zebularine. In particular, the unbound fractions can be assumed equal and the ratio $N_{HH}/N_{MM}$ assumed equal to the ratio $N_{MM}/N_{MS}$ to the power $-0.06$. Application of these equations is illustrated in Fig. 5 where measurements from the mouse ($M_{MS} = 0.02$ kg) and monkey ($M_{MK} = 3.5$ kg) have been scaled to the human ($M_H = 70$ kg) and compared with corresponding measurements. It can be seen that the agreement is good and very supportive of the theory.

With regard to toxic doses, Ryan and colleagues (19) have reported studies on monkeys where no signs of toxicity were observed for twice-weekly i.v. bolus doses of $58$ mg/m$^2$ per week over a period of 4 weeks. It is of interest to use the present theory to determine the scaled value of this dose for humans. With the results leading to the scaling predictions shown in Fig. 5, and with the dosing interval for the monkey as $\Delta_{TM} = 0.5$ week, Eq. M gives the value of the corresponding interval for the human as $0.91$ week, and Eq. I gives the dose for the human as $84.6$ mg/m$^2$ per week, or $77$ mg/m$^2$ for each of the 8 intervals.

(d) Combination chemotherapy. In the case where two or more anticancer agents are combined for improved therapy, the scaling theory is more involved. Scaling is, however, still possible under special circumstances. This matter is illustrated here for the case of combination chemotherapy with capecitabine and bevacizumab. With combination chemotherapy, it is generally required that the agents do not interact with one another, that their basic processes for therapeutic action are different, and that their toxicities do not overlap. This is the case with capecitabine and bevacizumab.
In considering dosage scaling so as to provide similar exposure of the combination of agents (independent of body size), Eq. K may first be considered to describe the concentrations of capcitabine by tagging the variables $D$, $t$, $U$, $N$, and $n$, as well as the function $f$, in this relation with subscript $C$. Likewise, for the description of the concentration of bevacizumab, the same may be done using subscript $B$. Now, for similarity of exposure, both descriptions must depend on the same variables. This can be done by including the following additional ratios in the functions $f_C$ and $f_B$ of each description:

$$\frac{N_B}{N_C}, \frac{U_B}{U_C}, \frac{\Delta t_B}{\Delta t_C}, \frac{n_B}{n_C}$$

(Quasi-constants)

For example, in the second description, the variable $t/N_B T$ may then be changed to $t/N_C T$ by multiplying by the first of the above ratios. Similar changes can be made for the remaining variables using one or more of the ratios (but, in all cases, keeping all the ratios in both functions). Analogous to the treatment used in establishing Eqs. L and M from Eq. J, the ratios in the functions $f_C$ and $f_B$ are required to be fixed in value in the scaling process. The following scaling relations for the agent capcitabine, like Eqs. L and M, may thus be written as:

$$\left( \frac{M_{BC}}{S} \right)_H = \left( \frac{U_{CM}}{U_{CH}} \right) \left( \frac{N_{CM}}{N_{CH}} \right)^2 \left( \frac{M_{BC}}{S} \right)_M$$

(Qa)

$$\left( \frac{\Delta t_C}{\Delta t_M} \right)_H = \left( \frac{N_{CH}}{N_{CM}} \right) \left( \frac{M_H}{M_M} \right)^{1/4}$$

(Qb)

subject to the conditions on the first two ratios that

$$\frac{N_B}{N_C}_H = \left( \frac{N_B}{N_C} \right)_M$$

and

$$\frac{U_B}{U_C}_H = \left( \frac{U_B}{U_C} \right)_M$$

(T)

Consistent with earlier requirements of Eq. K and its generalization here, the number of doses for each agents must also be the same for the human and laboratory animal, although the number may of course be different for the two agents. This condition then automatically satisfies the requirement for fixed value of the last of the above ratios.

Two similar equations can be written for the agent bevacizumab and, on using the first three of the above ratios, these two equations may conveniently be rewritten as:

$$\left( \frac{M_{IB}}{S} \right)_H = \left( \frac{M_{IB}}{S} \right)_M \left( \frac{M_{IC}}{S} \right)_M^{-1} \left( \frac{M_{IB}}{S} \right)_H$$

(R)

subject to the conditions on the first two ratios that

$$\frac{N_B}{N_C}_H = \left( \frac{N_B}{N_C} \right)_M$$

and

$$\frac{U_B}{U_C}_H = \left( \frac{U_B}{U_C} \right)_M$$

(S)

This scaling theory may be applied to the study by Kolinsky and colleagues (20) where, in addressing the matter of combination therapy involving capcitabine and bevacizumab, laboratory studies were made on mice having tumors formed from implanted cancer cells. With dosing schedule of 2-week cycles (7-day dosing followed by 7-day rest), capcitabine was administered (p.o.) once a day for 7 days of each treatment week with a dose of 1,360 mg/m$^2$ per day, and bevacizumab was administered (i.p.) twice weekly (1st and 4th injections) of each treatment week with a dose of 14.6 mg/m$^3$, or average of 4.17 mg/m$^2$ per day. Tumor volume at the beginning of treatment was approximately 100 mm$^3$. At the end of the treatment week of the second cycle, tumor volume had increased by a factor of 4 when capcitabine alone was used, whereas no increase occurred when bevacizumab was included. In contrast, the tumor volume in mice receiving no treatment increased by a factor of 15. These results are impressive and it is of interest to determine the corresponding scaled doses and schedule for the human.

First, it can be seen that Eq. T is essentially satisfied here, as it was found earlier in the individual studies of capcitabine and bevacizumab that $U_C$ and $U_B$ could be considered independent of body mass and $N_C$ and $N_B$ could be considered to vary with body mass to the powers −0.08 and −0.06, respectively, that is, with body mass to the value of about −0.07. Next, the scaled values of the dose and interval of capcitabine for the human ($M_H = 70$ kg) may be determined from Eqs. P and Q and the above values for the mouse ($M_M = 0.025$ kg) as 4,130 mg/m$^2$ per day for intervals of 4.17 days. The dose per interval is the product of these two values and is 17,200 mg/m$^2$. With 7 intervals, the total period of dosing for the human is also found to be 29.2 days. For bevacizumab, Eqs. R, Eqs. S, Eqs. T provide corresponding values for the human of 12.7 mg/m$^2$ per day over 29.2 days, with 185 mg/m$^2$ given at 1st and 4th injections of capcitabine.
Discussion

The concept of using body surface area for scaling critical doses of anticancer drugs from laboratory animals to humans and among humans of different sizes has been in place now for some 50 years. Limitations on its applicability have, however, not yet been identified in a systematic manner. The present work has been concerned with this subject within the larger context of developing scaling laws for single and periodic dosing. Scaling laws for projecting critical doses of anticancer drugs from laboratory animals to humans and among humans of different sizes have been considered in terms of the requirement of similarity of the concentration-time history of a particular agent. These indicate appropriate dosage scaling on the basis of body surface area provided adjustments are made for complex drug behavior involving plasma protein binding and cycles of blood circulation needed for adequate capillary exchange. In the case of single dosing, a further adjustment for body mass is needed for scaling dose itself, and for periodic dosing rate, an accompanying scaling restriction on drug schedule is required. In this case, dose per interval (or per injection) is determined by the product of dose rate (mg/m² per day) and dosing interval (time between doses). Application and extension of these scaling laws have already been discussed here in some detail. It is, however, worthwhile to consider briefly some further matters regarding the particular case of dosing of humans, where reference is to a standard human and associated standard dose.

Dosing of adult humans

Some simplification of the above general relations may be considered for scaling between adult humans because of the limited range of body sizes that are involved. In particular, the effects of complex drug behavior, mentioned above, may likely be neglected so that Eq. 1 can be reduced to the general requirement of dosage scaling on the basis of body surface area. Also, because the range of body masses is relatively small, no significant adjustment is likely to be required by Eq. M for drug schedule, so that the entire scaling procedure here is like that of standard clinical practice.

Pediatric dosing

Based on the present work, it can be anticipated that scaling of both drug dose and schedule will generally be important in pediatric dosing. For example, for the case of a standard human with a body mass of 60 kg and a drug similar, say, to zebularine, but with a standard dose of 20 mg/m² per day for 5 days, the dose per day for a small child with a body mass of 10 kg is 16.7 mg/m² per day, and the interval between injections is 0.70 day. The dose per interval (and injection) is therefore 11.7 mg/m², and this is to be given every 0.70 day for 5 injections, with a total dose of 58.5 mg/m². This dose may be compared with the more intense dosing based solely on body surface area, which requires a daily dose of 20 mg/m² per day for 5 days, with a total dose of 100 mg/m². Thus, dosing on the basis of body surface area alone is predicted here to result in significant overdose in small children, by a factor of 1.7. This result is in general agreement with experience, as reported by Johnson (21) for a wide variety of drugs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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