Scaling Adult Doses of Antifungal and Antibacterial Agents to Children

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My general pharmacokinetic scaling theory is discussed for the important matter of determining pediatric dosing for existing and new therapeutic drugs when optimal, or near-optimal, dosing for adults is known. The basis for the scaling is the requirement of a time-scaled likeness of the free-drug concentration time histories of children and adults. Broad categories of single and periodic dosing are considered. The former involves the scaling of dosage, and the latter involves both the dosage and schedule. The validity of the scaling relations is demonstrated by using measurements from previously reported clinical trials with adults and children (with ages generally 1 year or older) for the relatively new antifungal agent caspofungin and for the relatively new antibacterial agent linezolid. Standard pharmacodynamic effectiveness criteria are shown to be satisfied for the scaled dosage and schedule for children to the same extent that they are for the referenced adult. Consideration of scaling from adults to children is discussed for the case of new agents where no pediatric data are available and needed parameters are determined from *in vitro* measurements and preclinical animal data. A connection is also made between the allometric representation of clearance data and the dosing formulas. Limitations of the scaling results for infants because of growth and maturational matters are discussed. The general conclusion from this work is that the scaling theory does indeed have application to pediatric dosing for children, for both confirmation and refinement of present practice and guidance in pediatric treatment with new therapeutic agents.

Invasive fungal and bacterial infections are important causes of morbidity and mortality in children with cancer, as aggressive chemotherapy, stem cell transplantation, and other treatments weaken their immune systems and make them far more vulnerable than otherwise. Fortunately, improvements in antifungal and antibacterial agents over the past few years offer promise for increasingly successful therapy in such cases.

Clinical trials defining the efficacy and safety of new therapeutic drugs are, however, always carried out first with adults, and corresponding results directed specifically toward pediatric patients generally lag behind those for the adult population by several years. In the interim, a requirement therefore exists for the accurate scaling of effective drug doses from adults to children for guidance in pediatric treatment and clinical trials.

Formulas with the dose assumed to be proportional to body mass or body surface area generally fail to meet this need fully (3, 12). A description based on the assumed proportionality of dose and drug clearance likewise fails to provide a general representation because of the dependence of clearance on body size and the particular drug (14–16). The goal of the present work is thus to describe an alternative to these methods that can indeed meet the above-noted requirement for new agents as well as provide a possible improvement of the dosing of agents already in use in practice.

In a recent paper, I in fact presented a new scaling theory for projecting dosing regimens of anticancer drugs from small mammals to humans (4). The theory is based on the scaling characteristics of the fundamental governing physiologic processes and on the requirement of time-scaled similarity (or likeness) in the free drug concentration-time histories of humans and mammals. A brief note was made previously of the possible application of the theory to the important but not-well-understood matter of scaling reliable adult doses to children. A detailed consideration of this topic accordingly forms the subject of the present paper. Because of complex maturational matters concerning newborns and in-

fants (11, 16), attention is restricted generally to children aged 1 year or older.

Fundamentals of the theory and its application are examined and confirmed with results from work reported previously by Walsh et al. (25) and Neely et al. (20) regarding the relatively new antifungal agent caspofungin and from work reported previously by Jungbluth et al. (13) and Stalker et al. (24) for the relatively new antibacterial agent linezolid. Matters of effectiveness are considered, and standard pharmacodynamic criteria are shown to be satisfied for scaled dose and schedule for children to the same extent as that for the referenced adult. Additional topics are discussed, including the significance of plasma protein binding, the use of preclinical animal data for pediatric scaling when required, the limitations of the application of the scaling theory to infants because of immature clearance paths, and the connection of dosing formulas with allometric descriptions of clearance variables.

The basic nomenclature is as follows: body mass (M), blood volume (V_B), drug dose (D), and drug concentration in plasma (C). With respect to the latter parameter, plasma volume and blood volume are assumed to be proportional under the change in size from adults to children so that no special designation is required for scaling purposes. Additional variables are defined as needed.

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MATERIALS AND METHODS

Data used for the agent caspofungin were mainly the measurements reported previously by Walsh et al. (25) and Neely et al. (20) for the time history of plasma drug concentrations for toddler (average age, 15 months), child (average age, 7 years), adolescent (average age, 14 years), and adult (18+ years of age). Drug concentration measurements were given in those publications in a graphical form and consisted of averaged data from several patients within each category. The data used here were taken from enlargements of the original figures. Averaged body masses associated with the averaged concentration data were not reported and were estimated from the data given. Values of pharmacokinetic (PK) variables were determined from the average concentration data and contrasted with reported averages from individual data sets for appropriateness before use in analysis. Drug concentration data from preclinical studies with monkeys were taken from tabulated data and enlargements of graphically presented data reported previously by Sandhu et al. (21) for the illustration of the use of the theory without pediatric measurements.

Data used for the agent linezolid consisted of half-life and clearance measurements for children and adults, as summarized previously by Jungbluth et al. (13). Average body masses were taken from data reported previously by Mahmood (15). Concentration data were taken from enlargements of graphical data presented previously by Stalker et al. (24).

The overall approach of the present work involves a brief review of my scaling theory, with some clarifying remarks on its original presentation and with an examination of its basic concepts and predictions using the above-noted measurements for the indicated agents. The scaling theory itself involves a simple mathematical description of the drug concentration in terms of the basic quantities on which it depends and the extraction of required scaling laws from the description.

The method may be illustrated in a simple form by considering the maximum (backward-extrapolated α -phase) concentration, C_0 (units of mass per volume), of a given drug when a dose, D (units of drug mass per body mass), is administered by an intravenous (i.v.) bolus injection. Simple considerations indicate that the concentration C_0 must depend on the dose, D , chosen and on the volume of blood, V_B , involved. Mathematically, C_0 can thus be regarded as an unknown function of D and V_B , but as discussed below, it must also depend on body mass, M (units of mass), and blood density, ρ (units of mass per volume), in order to make the relation independent of any particular measuring units chosen for the individual variables. Thus, with C_0 assumed to be proportional to D for a fixed size, the general relation is then expressible as

$$\frac{C_0 V_B}{DM} \propto f\left(\frac{\rho V_B}{M}\right) \quad (1)$$

where the symbol $\propto$ denotes proportionality under a change in size where $f(-)$ denotes a general function and where, as required, the two ratios are independent of particular units used, since $C_0 V_B$ and DM both have same units (mass), and similarly, ρV_B and M both have same units (again mass). The scaling equations are thus found as follows: if $\rho V_B/M$ is set equal to a fixed constant, then $C_0 V_B/DM$ must also equal a fixed constant. Evaluating the constants with adult values (denoted with a subscript A) and recognizing that the blood density, ρ , is a fixed constant independent of size, the following tentative relations for children (denoted with a subscript P) may be obtained:

$$\left(\frac{C_0}{D}\right)_P = \left(\frac{C_0}{D}\right)_A \text{ for } \left(\frac{V_B}{M}\right)_P = \left(\frac{V_B}{M}\right)_A \quad (2)$$

Now, for mammals in general and humans in particular, blood volume and body mass are proportional under a change in size so that the second relation is satisfied automatically for these cases and the first relation then requires the ratio C_0/D to be independent of size, consistent with experience. This approach is used below for the case of the time history of drug concentrations.

RESULTS

Scaling theory for single-bolus dosing. The fundamentals for the scaling theory for dosage and related time history of drug concentrations in the blood were discussed previously (4–6). Details are described in the appendix and can be summarized here as follows. An i.v. bolus (or near-bolus) injection of the drug is first envisioned, followed by back-and-forth capillary exchange with surroundings as the blood circulates. Accompanying this is a tendency toward a uniform distribution of the drug, with all the drug passing through the capillary walls after a few cycles, N , of blood circulation, with each cycle requiring time T_B . Considering, for example, basic units of mass (g), volume (ml), and time (seconds), the drug concentration C ($\mu\text{g/ml}$) at time t (seconds) can accordingly be expected to depend on the net inward flow, Q (ml/s), across the capillary walls; the net circulation time, NT_B (seconds); the dose mass, M_D (mg), per unit of body mass M (kg); and the blood volume, V_B (ml). The resulting equation must be expressible in a dimensionless form so as to be independent of any particular choice of measuring units. With the relative dose, M_D/M , denoted by D (mg/kg of body weight), the general relation is accordingly that the ratio CV_B/DM must vary with the two ratios QNT_B/V_B and t/NT_B .

To limit attention to the effective part of the drug remaining after plasma protein binding, the fraction, U , of the available drug dose can be included as a multiplier of the dose, D . Using the known condition that the blood volume, V_B , and the body mass, M , are proportional for different-size humans and assuming proportionality between concentration and inflow, the expression for the concentration of unbound drug in the blood can thus be written in terms of the general function $f(t/NT_B)$, as follows:

$$\frac{C}{UD} \propto \frac{QNT_B}{M} f\left(\frac{t}{NT_B}\right) \quad (3)$$

The function $f(-)$ in equation 3 can generally be expected to be different for different drugs. Also, the factor N (referred to here as the circulation factor) can generally be regarded as being dependent on both body size and drug characteristics. While developed for i.v. injection, equation 3 can also be expected to apply for oral administration with an adequate bioavailability and absorption rate.

The scaling theory developed in previous work (7–9) requires that the flow, Q , across capillary walls must vary with body mass to the power of 5/6 and that the time for circulation, T_B , must vary as body mass to the power of 1/4. Thus, the ratio QT_B/M in equation 3 must vary with body mass raised to the power of 1/12. Accordingly, when the ratio t/NT_B in the function $f(-)$ of equation 3 is held fixed, the value of the function must itself be fixed, and the ratio on the left-hand side of equation 3 must be proportional to the first ratio on the right-hand side. The scaling laws relating the drug concentration for the pediatric patient (subscript P) and adult patient (subscript A) may accordingly be written as follows:

$$\left(\frac{C}{D}\right)_P = \frac{U_P}{U_A} \frac{N_P}{N_A} \left(\frac{M_P}{M_A}\right)^{1/12} \left(\frac{C}{D}\right)_A \quad (4)$$

$$t_P = \frac{N_P}{N_A} \left(\frac{M_P}{M_A}\right)^{1/4} t_A \quad (5)$$

Scaling drug dose. Significant results associated with scaling laws for drug dosage follow from the above-mentioned description of plasma concentrations. The similarity condition related to

the requirement for drug dose scaling is assumed to be that the free plasma concentrations, C , of children and adults must be the same at the corresponding times t/NT_B . Here, the use of the latter ratio rather than time alone is required in order to take into account the different rates of operation governing physiologic processes of children and adults, with the product NT_B being regarded as a characteristic time for a given body size and a given drug. The dosage requirement, D , for this “similar-exposure” condition follows from equation 3 and is expressible, with M_D/M written for D , as

$$\left(\frac{M_D}{M}\right)_p = \frac{U_A}{U_p} \frac{N_A}{N_p} \left(\frac{M_A}{M_p}\right)^{1/2} \left(\frac{M_D}{M}\right)_A \quad (6)$$

or, in terms of dose per unit of body surface area, S , as

$$\left(\frac{M_D}{S}\right)_p = \frac{U_A}{U_p} \frac{N_A}{N_p} \left(\frac{M_p}{M_A}\right)^{1/4} \left(\frac{M_D}{S}\right)_A \quad (7)$$

with S assumed to be proportional to body mass to the two-thirds power and with the proportional coefficient equal to $0.108 \text{ m}^2/\text{kg}^{2/3}$ when needed for unit conversion (see the appendix).

Scaling total concentrations. Equations 4 to 7 and the underlying relation depicted in equation 3 apply to the free concentration, C , associated with the fraction of available drug dose in the blood, but similar expressions can be developed for the total concentration, C_T , as normally measured. This involves the recognition for the relation depicted in equation 3 that a reduction in the dose of amount U can be considered alternatively as a reduction in the total concentration, C_T . Thus, UD and C in this relation can be replaced by D and UC_T , respectively, so that

$$\frac{UC_T}{D} \propto \frac{QNT_B}{M} f\left(\frac{t}{NT_B}\right) \quad (8)$$

Equations like equations 4 and 5 for the total concentration are then found to be expressible as follows:

$$\left(\frac{C_T}{D}\right)_p = \frac{U_A}{U_p} \frac{N_p}{N_A} \left(\frac{M_p}{M_A}\right)^{1/2} \left(\frac{C_T}{D}\right)_A \quad (9)$$

$$t_p = \frac{N_p}{N_A} \left(\frac{M_p}{M_A}\right)^{1/4} t_A \quad (10)$$

The first formulation involving the above-described equations 3 to 5 is primarily of interest in establishing formulas relating adult and pediatric dosing regimens of therapeutic drugs. The second formulation, involving equations 8 to 10, is useful for dealing directly with measured concentration data. The second formulation is convenient but not essential, as measured total concentrations can be converted to free concentrations (with a known fraction of free concentrations) for use with equations 4 and 5, and the results can then be converted back to total concentrations for further considerations.

Connection between relations. The relations depicted in equations 3 and 8 can be connected by using the well-known equation $C = fu \times C_T$, where fu denotes the usual fraction of the available (free) concentration. Thus, these relations require UD to be proportional to the product $fu \times D/U$ so that U must be proportional to $\sqrt{fu}$, and the following equation must apply:

$$\frac{U_p}{U_A} = \sqrt{\frac{fu_p}{fu_A}} \quad (11)$$

In using the present theory, the ratio U_p/U_A may be deter-

mined directly from the latter equation by using independently measured values of fu_p and fu_A . Alternatively, it may be established from a best-fit study of the concentration data, as has been done in the present work.

PK variables. Directly connected with the scaling of concentration data are the scaling laws for various pharmacokinetic (PK) variables. These variables follow from the above-described work and are developed in the appendix. They may be summarized as follows. With all variables based on the total concentration, any PK time variable, T , such as half-life, must scale as

$$T_p = \frac{N_p}{N_A} \left(\frac{M_p}{M_A}\right)^{1/4} T_A \quad (12)$$

any PK volume variable, V , such as the volume of distribution, must scale as

$$V_p = \frac{U_p}{U_A} \frac{N_p}{N_A} \left(\frac{M_p}{M_A}\right)^{11/12} V_A \quad (13)$$

and the clearance, CL , must scale as

$$CL_p = \frac{U_p}{U_A} \left(\frac{N_A}{N_p}\right)^2 \left(\frac{M_p}{M_A}\right)^{2/3} CL_A \quad (14)$$

For the case of simple drug behavior (the factors U and N are the same for child and adult), it can be seen that times, T ; volumes, V ; and clearance, CL , must scale with body mass to powers of $1/4$, $11/12$, and $2/3$, respectively. Without the ratio U_p/U_A in the equations, irrespective of its individual value, these scaling relations also apply for the PK variables, as determined from free concentrations, with the drug dose considered $U \times D$, as presented in my previous work (4). Time variables such as half-life depend only on ratios of concentration values and thus are independent of protein binding. They accordingly apply to both total and free concentrations without adjustment.

Examination of theory—part I. The adequacy of the above-described scaling theory for a single i.v. bolus (or near-bolus) dose can be examined by using detailed results from the first cycle of daily dosing of the antifungal agent caspofungin, as reported previously by Walsh et al. (25) and Neely et al. (20) and as referred to above. Pediatric patients in those studies were grouped according to the ages 7 to 24 months, 2 to 11 years, and 12 to 17 years and were classified as toddler, child, and adolescent, respectively. Average ages for these categories were reported to be 15 months, 7 years, and 14 years, respectively. The average body mass for toddlers is assumed to be 11 kg, based on a reported range of between 9.4 and 11.9 kg. Specific body mass data for children and adolescents were not reported, but data for body mass versus age have been determined from ratios of reported values of clearance and clearance per body mass for all 39 children involved in the study, with averages of these values shown in Fig. 1.

The data shown in Fig. 1 are assumed to be representative of the average measurements for children (total of 10 patients) and adolescents (total of 8 patients). Average body masses for children and adolescents of 21 kg and 57 kg, respectively, are accordingly assumed here. Body masses for adults may similarly be expected to be within the range of 65 to 75 kg, with a typical value of 70 kg.

The dosing for the pediatric patients was generally based on body surface area, with i.v. administered doses of 50 mg/m^2 over a 1-h period every 24 h for a total of 4 days. The dosing for adults in the study was 50 mg per day (0.71 mg/kg per day) for 9 days, with a 1-h period of i.v. administration every 24 h.

FIG 1 Body mass data from a caspofungin study described previously (25). The curve is the standard 50th percentile variation.

In applying the present theory to results from these studies, it is necessary to first determine the size dependence of the characteristic time of the drug and related physiologic response, as represented in the theory by the product of the circulation number, N , and time, T_B , for a cycle of blood circulation. This matter is conveniently handled by examining the half-life time, $T_{1/2}$, for β -phase exponential decay, as found here from average concentration data reported previously (20, 25). Values so determined for toddler, child, adolescent, and adult are 7.7 h, 8.0 h, 10.6 h, and 11.4 h, respectively, compared with similar reported averaged values from individual data sets of 7.8 h, 8.0 h, 10.5 h, and 12.0 h, respectively. Figure 2 shows the half-life values for the pediatric and adult patients for associated body masses considered here. Also shown is a representative equation showing variation with body mass raised to the $1/4$ power, with a coefficient of determination, r^2 , of 0.95, indicative of an excellent description.

These results may be considered in connection with equation 12, where, with adult values considered to be fixed, the relation indicates that the half-life is proportional to the product of the circulation number, N , and body mass, M , raised to the $1/4$ power. Upon comparing this relation with the empirical equation shown in Fig. 2, it can therefore be seen that the circulation number, N , for caspofungin must, for consistency, be assumed to be independent of body mass and, hence, independent of patient size.

The set of relations for scaling total concentrations at various times for caspofungin is that given by equations 9 and 10, with N_p

FIG 2 Half-life data for caspofungin for children and adults after single i.v. dosing. Data are based on data reported previously (20, 25).

FIG 3 Scaling of total concentration data for caspofungin during the first day of multiple i.v. injections. Basic data are from data reported previously (20, 25). Expanded units for the vertical axis are $\mu\text{g}/\text{ml}$ per mg/kg .

equaling N_A , as established above. The additional tentative assumption that U_p equals U_A will also be made here for preliminary investigations. Drug concentration measurements for the adult (dose of 0.71 mg/kg) and toddler (dose of 2.4 mg/kg) are accordingly shown in Fig. 3, together with results from scaling the data from adult to toddler using the above-described simplified version of equations 9 and 10. It can be seen that the results shown in Fig. 3 are impressive in that all values scale very closely to those measured for the toddler. Similar results are found for scaling adult measurements to measurements for adolescent and child with the same restrictions on equations 9 and 10. These restrictions ($N_p = N_A$ and $U_p = U_A$) thus allow caspofungin to be characterized as showing simple drug behavior (4).

Note that the scaling theory requires strictly that the infusion time for the toddler scale like other times rather than equal the adult (1 h) time indicated in Fig. 3. Fortunately, however, the error is generally negligible for near-bolus injections, as considered here.

In addition to the study of scaling of concentration data, it is of interest to investigate the scaling of drug dose for caspofungin, as expressed by equations 6 and 7. The fundamental basis for these equations is that the predicted dose should provide a matching of the free drug concentration-time history of the pediatric and adult patients when adult times are scaled to pediatric times. Thus, when equations 6 and 7 apply, equation 4 requires that C_p equal C_A for the times given by equation 5.

Figure 4 shows such an agreement, as found in the present work. The free concentration variation of caspofungin for the adult is shown, based on a dose of 0.71 mg/kg and a free concentration fraction of 0.03 (generally accepted for caspofungin for both adults and children). The adult times for these concentrations were scaled to toddler times by using equation 4, thus providing the adult standard indicated. From equation 6 and an adult dose of 0.71 mg/kg , it can be found that the required dose for the toddler is 0.83 mg/kg . The associated free concentrations for the toddler can thus be obtained from the data shown in Fig. 3 by multiplying by this dosage value and by the free concentration factor of 0.03. Results of these calculations are shown in Fig. 4 and are denoted as toddler (adjusted dose). It can be seen that these concentration data agree very well with the adult standard, consistent with equations 3, 6, and 7.

FIG 4 Free concentration data for caspofungin showing the agreement of toddler data (dose of 0.83 mg/kg) with the adult standard for a dose of 0.71 mg/kg, based on data reported previously (20, 25).

Scaling theory for multiple-bolus dosing. Attention may next be directed to periodically administered doses, with the rate of drug dose, D^R (in units of, say, mg/kg per day), defined as $\Delta D/\Delta t$, where Δt (units of, say, days) denotes the interval between injections of amount ΔD (expressed per unit of body mass, as described above). In the usual way, Δt and the total number of injections, say, n , define the schedule for dosing.

The scaling law for the rate of the drug dose for the pediatric patient, in terms of that for the adult, can be determined from the basic relation depicted in equation 3 when D is replaced by $D^R\Delta t$ and the function $f(-)$ is expanded to include the ratio $\Delta t/NT_B$ and the number, n , of doses given. Thus,

$$\frac{C}{D^R\Delta t} \propto \frac{UQNT_B}{M} f\left(\frac{t}{NT_B}, \frac{\Delta t}{NT_B}, n\right) \quad (15)$$

Scaling drug dose. The similarity condition for periodic drug dosing is an expanded version of that for single dosing, namely, that the free plasma concentrations, C , of children and adults must be the same at corresponding times t/NT_B when the ratio $\Delta t/NT_B$ and the number of doses, n , are fixed.

Requirements for the similar-exposure conditions can be determined in a manner like that described above for obtaining relations depicted in equations 6 and 7. The general scaling equation for the dose rate per unit of body mass, D^R (dose rate, M_D^R , divided by body mass, M), is found from equation 15 to be expressible as

$$\left(\frac{M_D^R}{M}\right)_p = \frac{U_A}{U_p} \left(\frac{N_A}{N_p}\right)^2 \left(\frac{M_A}{M_p}\right)^{1/3} \left(\frac{M_D^R}{M}\right)_A \quad (16)$$

or, in terms of dose rate per unit of body surface area, S , as

$$\left(\frac{M_D^R}{S}\right)_p = \frac{U_A}{U_p} \left(\frac{N_A}{N_p}\right)^2 \left(\frac{M_D^R}{S}\right)_A \quad (17)$$

with restrictions in both cases that n_p equals n_A and

$$\frac{\Delta t_p}{\Delta t_A} = \frac{N_p}{N_A} \left(\frac{M_p}{M_A}\right)^{1/4} \quad (18)$$

where n_p and n_A denote the number of doses administered for pediatric and adult patients, respectively, and Δt_p and Δt_A denote the corresponding intervals between dosings.

It is interesting that equation 17 shows for simple drug behavior ($U_A/U_p = N_A/N_p = 1$) that the dose rate per unit of body surface area is independent of body size. This dosing condition has generally been assumed in oncology for all anticancer drugs and was adopted previously by Walsh et al. (25) and Neely et al. (20) in their investigations of caspofungin, as discussed here.

Upon recognizing that the product $M^R\Delta t$ denotes the dose ΔM_D per interval, the following relation can be written using equations 16 and 18:

$$\left(\frac{\Delta M_D}{M}\right)_p = \frac{U_A}{U_p} \left(\frac{N_A}{N_p}\right) \left(\frac{M_A}{M_p}\right)^{1/2} \left(\frac{\Delta M_D}{M}\right)_A \quad (19)$$

which, with equations 17 and 18, is also expressible in terms of body surface area as

$$\left(\frac{\Delta M_D}{S}\right)_p = \frac{U_A}{U_p} \frac{N_A}{N_p} \left(\frac{M_p}{M_A}\right)^{1/4} \left(\frac{\Delta M_D}{S}\right)_A \quad (20)$$

The latter equations are like equations 6 and 7 for single dosing except that, now, the left-hand side refers to the dose per interval, with the latter being defined by equation 18. The recognition that the scaling of the dose should be accompanied by the scaling of the time interval between dosing was discussed previously by Mor-denti (17).

In application, with the body mass of adult given and the dose per interval specified, equation 19 or 20 may be used to determine the dose per interval for a pediatric patient of a given body mass, and equation 18 may be used to determine the interval, Δt_p , between dosing. Alternatively, equation 16 or 17 may be used together with the dosing interval to determine the dose per interval.

Scaling total concentrations. In the same manner as that used to obtain equations 9 and 10, the scaling laws for measured total concentrations for periodic dosing can be developed by replacing C with UC_T on the left-hand side of equation 15 and deleting the factor U on the right-hand side. The resulting relations for scaling total concentrations then take the form shown below by equations 21 to 23:

$$\left(\frac{C_T}{D^R}\right)_p = \frac{U_A}{U_p} \left(\frac{N_p}{N_A}\right)^2 \left(\frac{M_p}{M_A}\right)^{1/3} \left(\frac{C_T}{D^R}\right)_A \quad (21)$$

at times

$$t_p = \frac{N_p}{N_A} \left(\frac{M_p}{M_A}\right)^{1/4} t_A \quad (22)$$

with

$$\Delta t_p = \frac{N_p}{N_A} \left(\frac{M_p}{M_A}\right)^{1/4} \Delta t_A \quad (23)$$

and with the general restriction that n_p equals n_A .

It may be noted that equation 21 can be replaced by the above-described equation 9 provided that the dose, D , in that equation is replaced by the dose per interval, ΔD , given by equation 19. This can readily be found to be the case by substituting $\Delta D/\Delta t$ for D^R in equation 21 and using equation 23.

Examination of theory—part II. Continuing with the study of the antifungal agent caspofungin, the measurements from the same works by Walsh et al. (25) and Neely et al. (20) noted above may be used to demonstrate the applicability of the scaling theory for periodic dosing. From the above-described work with single dosing, it can be expected that equations 21 to 23 will apply with N_p equal to N_A and with U_p equal to U_A (simple drug behavior).

FIG 5 Scaling results for toddler (fourth day) after daily dosing of caspofungin. Basic data were reported previously (20, 25). Expanded units for the vertical axis are $\mu\text{g}/\text{ml}$ per $(\text{mg}/\text{kg})/\text{day}$.

Total concentration data are available for the toddler, child, and adolescent during the fourth day of daily dosing of $50 \text{ mg}/\text{m}^2$ and for the adult during the ninth daily dosing of 50 mg per day. The success of the theory is illustrated in Fig. 5, where scaling results (from adult to toddler) are shown and compared with direct measurements for the toddler.

The requirement of equation 23 for the dosing interval has not been met for the comparisons shown in Fig. 5, as all measurements were for the adult interval of 24 h rather than the corresponding 15 h strictly required for the toddler as determined by equation 23. The agreement between the scaled and measured values accordingly indicates, in the present case, the relative insensitivity of the dosing interval in scaling (though not necessarily in effectiveness).

In addition to interval considerations, strict similarity in dosing also requires that the number of injections (at the time of measurement) be the same for both actual and scaled data. This condition is also not satisfied for the data sets represented in Fig. 5, as the measurements for the toddler are for the fourth day of dosing and those for the adult data are from the ninth day. The good agreement between the two data sets may thus be interpreted as meaning that approximate steady-state conditions prevailed after the first 3 injections so that the actual number ceased to be significant.

Dosage calculations. With respect to dosage calculations, the formula for the dose rate is equation 16 or 17, depending on whether body mass or body surface area is used. The use of either of these equations implies that free drug concentrations for the pediatric patient will be the same as those for the adult patient at appropriately scaled times. This may be demonstrated by using the data shown in Fig. 5 together with the governing relations of equations 16 to 18 and a modified version of those of equations 21 to 23, where equation 21 is replaced by the free concentration condition $C_p = C_A$ associated with equations 16 to 18.

Free concentration measurements for the adult have accordingly been found from data shown in Fig. 5 by multiplication by an adult dose rate of $0.71 \text{ mg}/\text{kg}$ per day and by a free concentration factor of 0.03 for adults and children, as described above in connection with results shown in Fig. 4. Equa-

FIG 6 Free concentration data for caspofungin showing the agreement of toddler data (dose rate of $1.3 \text{ mg}/\text{kg}$ per day) with the adult standard (dose rate of $0.71 \text{ mg}/\text{kg}$ per day), based on data reported previously (20, 25).

tion 22 was then used to scale the adult times for these concentrations to toddler times. Results are shown in Fig. 6 and are denoted as adult standard.

Equation 16 provides a scaled dose rate for the toddler of $1.3 \text{ mg}/\text{kg}$ per day for the specified dose rate for the adult ($0.71 \text{ mg}/\text{kg}$ per day). Associated free concentration data for the toddler have thus been determined from the data shown in Fig. 5 by multiplication by a dose rate of $1.3 \text{ mg}/\text{kg}$ per day and by a free concentration factor of 0.03. These results are shown in Fig. 6 and are denoted as toddler (adjusted dose). Good agreement with the adult standard can be seen to exist, consistent with the requirement of equations 16 to 18. As noted above for the results shown in Fig. 5, this agreement indicates an insensitivity of the strict conditions of a scaled interval and a fixed number of injections for this case.

Effectiveness of dosing. The implicit assumption of the present scaling work is that the effectiveness of a therapeutic drug for a pediatric patient will equal or exceed that for the adult when the pediatric free drug plasma concentrations equal those of the adult at relative times in the dosing interval. Based on pharmacodynamics, one or more of the following three requirements must be satisfied for this to be the case for any particular agent: (i) the ratio of the maximum free drug concentration (C_{max}) to the MIC (free) of the pediatric patient should equal or exceed that of the adult patient; (ii) the ratio of the average free concentration to the MIC value over the dosing interval (Δt) must equal or exceed that for the adult; and (iii) the time (Δt^*) per unit of dosing interval (Δt) that the pediatric free concentration exceeds the MIC value should equal or exceed that of the adult. For equal effectiveness, these conditions may be expressed as follows:

$$\left(\frac{C_{\text{max}}}{\text{MIC}} \right)_p = \left(\frac{C_{\text{max}}}{\text{MIC}} \right)_A \quad (24)$$

$$\left(\frac{\Delta \text{AUC}}{\Delta t \times \text{MIC}} \right)_p = \left(\frac{\Delta \text{AUC}}{\Delta t \times \text{MIC}} \right)_A \quad (25)$$

FIG 7 Half-life variation of linezolid with body mass. The equation is based on measurements for the child, adolescent, and adult. Basic data were reported previously (13).

$$\left(\frac{\Delta t^*}{\Delta t}\right)_p = \left(\frac{\Delta t^*}{\Delta t}\right)_A \quad (26)$$

In writing equation 25, use has been made of the fact that the average of the drug concentration over an interval can be expressed as the associated area under the concentration-time curve (ΔAUC) when divided by the interval itself. Also, if the value of the dosing interval, Δt , is the same for both adults and children, it need not be included in the relation (as is generally the case). Such a restriction is, of course, not part of the present scaling theory.

The MIC values in the above-described relations can be expected to be the same for children and adults so that these conditions involve only the free drug concentration-time histories of adult and pediatric patients. All three conditions are, in fact, then satisfied automatically with the use of the present scaling theory, because the free dose concentration-time histories of the pediatric and adult patients differ only by the scaling factor for time, and all three conditions are independent of time.

These conditions can be illustrated with the data shown in Fig. 6. Consistent with equation 24, the maximum concentrations for toddler and adult (0.26 $\mu\text{g/ml}$) can, in fact, be seen to be equal. For equation 25, the areas under the curves for the toddler and adult can be found to be about 1.5 $\mu\text{g} \cdot \text{h/ml}$ and 2.4 $\mu\text{g} \cdot \text{h/ml}$, respectively, and the associated intervals can be seen to be about 15 h and 24 h, respectively, so that the ratios 1.5/15 and 2.4/24 are essentially equal, as required. Also, considering equation 26 with an assumed (unbound) MIC value of, say, 0.10 $\mu\text{g/ml}$, the fraction of the interval time that the concentration is above the MIC value for the toddler and adult can be seen to be essentially equal (7/15 and 11/24, respectively), consistent with the required relation. Thus, matters of MIC and duration of action, if dealt with adequately for adults, will also be satisfied for children with scaled pediatric dosing based on the present theory.

Application to linezolid. Attention is next directed to the relatively new antibacterial agent linezolid, which has been shown to have significant activity against a number of otherwise drug-resistant bacteria. Jungbluth et al. (13) previously summarized values of pharmacokinetic parameters from the measured total concentration-time histories of this drug for infant (aged 28 days to 3 months), child (aged 3 months to 11 years), adolescent (aged 12 to

TABLE 1 Scaled values of clearance of linezolid from adult value

Patient	M (kg)	Scaled CL (ml/min) (measured CL)
Adult	70	119 (119)
Adolescent	55	109 (115)
Child	20	75 (76)
Infant	5	45 (27)

17 years), and adult. Average body masses associated with these data and age groups are taken from data reported previously by Mahmood (15) and are as follows: 5 kg for infant, 20 kg for child, 55 kg for adolescent, and 70 kg for adult.

Half-life values are illustrated in Fig. 7. The value for the infant is highlighted in the figure because clearance data indicate non-uniform size effects. The indicated best-fit equation (with body mass to the power of 0.40) and the associated predictions shown are based on data for child, adolescent, and adult only. It can be seen however, that the measurement for the infant is consistent with the predictions.

Based on these results, it can be seen from equation 12 that the ratio of circulation numbers N_p/N_A can be considered to vary with the ratio of body masses M_p/M_A to the power of 0.15. The scaling relation of equation 14 for clearance may thus be written in the following form, using $U_p/U_A = 1$ as a tentative assumption:

$$\text{CL}_p = \left(\frac{M_p}{M_A}\right)^{0.37} \text{CL}_A \quad (27)$$

Results from the use of equation 27 are shown in Table 1. Values for the measured clearance for pediatric and adult patients, as given previously (13), are also tabulated in Table 1. It can be seen that the calculations and measurements agree well with one another for the adolescent and child, thus supporting the assumption that U_p/U_A equals 1. However, an appreciable difference exists between the calculated and measured clearances for the infant, with the measured value being only about 60% of the theoretical value. This deviation is likely due simply to growth and maturational influences not present in older children, as mentioned above in the introduction, with reference to the work of Hayton et al. (11) and Mahmood (16).

Dose and schedule. The typical adult dose of linezolid presently recommended is 600 mg every 12 h for 14 to 28 days. In Table 2 are listed the corresponding predictions of pediatric doses per interval as well as intervals based on equation 19 and values for the ratio N_p/N_A , as determined from the above-described considerations. No predictions are given for the infant because of the deviation of its clearance from the scaling result, as indicated in Table 1. However, this is not assumed to be the case for the toddler, based on the above-described work with caspofungin, and associated predictions are included for comparative purposes.

TABLE 2 Theory-based possible pediatric dose (per interval) of linezolid with a fixed number of injections

Patient	M (kg)	ΔD (mg/kg)	Δt (h)
Adult	70	8.6	12
Adolescent	55	9.0	11
Child	20	11.5	7.3
Toddler	10	13.5	5.5

FIG 8 Free concentration data for linezolid for adult (65 kg) with dose of 8.0 mg/kg per interval of 12 h and corresponding predictions for child (20 kg) for scaled dose of 10.5 mg/kg per interval of 7.5 h. Data for adult based on previously reported measurements (24).

General recommendations for pediatric dosing of linezolid are 10 mg/kg every 8 to 12 h for 14 to 28 days (13, 18). It can be seen that the present theory and calculations shown in Table 2 (for both dose and interval) are in good agreement with these dosing recommendations. The dosing regimens for the child and toddler are particularly noteworthy because they indicate somewhat higher doses and shorter dosing intervals than presently recommended.

Effectiveness. The effectiveness of linezolid, when based on dosing requirements determined from the present scaling theory, can be illustrated in the same manner as that described above for caspofungin. The basic requirements assumed for an equal effectiveness for pediatric and adult patients are those relations given by equations 24 to 26. Free concentration data for the adult are shown in Fig. 8, as constructed from measurements described previously by Stalker et al. (24) and the use of a free concentration fraction of 0.69 (associated with the 31% protein binding reported previously by Jungbluth et al. [13]). Also shown are corresponding concentration data for the child, as determined by scaling the adult data using the present theory. Assuming, for example, a typical MIC (total) of 4 µg/ml, as reported and discussed previously by Gee et al. (10), the corresponding free concentration is 2.8 µg/ml, as indicated in Fig. 8.

With regard to equations 24 to 26, it can be found from the results shown in Fig. 8 that all are satisfied for identical pediatric and adult MIC values. In particular, equation 24 is satisfied since the maximum concentrations for child and adult are the same (10.5 µg/ml). Likewise, equation 25 is satisfied since the areas under the curves for child and adult are 38 µg · h/ml and 62 µg · h/ml, respectively, for corresponding dosing intervals of 7.5 h and 12 h, thus indicating essentially the same average concentrations for the child (38/7.5) and adult (62/12) of about 5 µg/ml. Also, equation 26 is satisfied since the times that the concentrations of the child and adult are above the critical MIC value are about 6 h and 9.5 h, respectively, with fractions of dosing intervals being

essentially the same for the child (6/7.5) and adult (9.5/12), about 0.80.

DISCUSSION

The purpose of this paper is to examine the applicability of my recently reported scaling theory to the important matter of scaling adult drug doses of antifungal and antibacterial agents to children. Attention has been directed specifically to the relatively new antifungal agent caspofungin and the relatively new antibacterial agent linezolid. Basic data from these studies regarding the time history of plasma concentrations or related variables are available. These data have been used here to confirm fundamental aspects of the theory and provide an endorsement of its validity. The following discussion provides some additional insight into the theory.

Application. A simple illustration of the applicability of the theory is provided by the calculation of the dose of caspofungin for a toddler when the adult dose is 150 mg per day rather than the normal 50 mg per day. Betts et al. (1) previously reported results from clinical trials for such “high-dose caspofungin” that indicated a safe and somewhat more effective response than with the normal dose. Interestingly, equations 17 and 18 show (for simple drug behavior with $M_p = 11$ kg and $M_A = 70$ mg) that the corresponding dose rate for the toddler is 82 mg/m² per day with a dosing interval of 0.63 days. Thus, the dose (per interval) is 52 mg/m² every 15 h. This dose is about the same as that presently recommended for daily dosing (50 mg/m²). However, more frequent dosing is required so that about 65% more drug would be given over a fixed number of days.

Age limitations. It is worthwhile to emphasize caution in applying the present scaling theory to the very young, as the immaturity of their physiologic processes can reduce or eliminate their similarity with older children and adults, as is needed to make the scaling work. Based on the successful application found here for toddlers (i.v. administration of caspofungin) with an age range of 10 to 22 months and the unsuccessful application found for infants (i.v. administration of linezolid) with an age range of 1 to 3 months, it appears appropriate to limit the theory generally to children aged 1 year or older.

Plasma protein binding. Another aspect of this work of interest concerns the role of plasma protein binding in dose determinations. As usually measured, protein binding involves the fraction f_u of the total drug concentration that is unbound and thus free for therapeutic purposes. It enters into the dosage formulas of the present work through the related free fraction U of the total drug dose. *In vitro* studies can provide values of f_u for children and adults for any given agent, and their ratio can be incorporated into the present scaling theory through the use of equation 11 to find the required ratio of the pediatric value, U_p , to the adult value, U_A . Alternatively, when concentration data are available for children, these may be used with the theory to determine the ratio U_p/U_A needed for dosage determinations. This approach was that used in the present work, where the ratio of free dose fractions was found to be equal to 1.0 for children administered standard doses of either caspofungin or linezolid.

Scaling new drugs to children. An additional matter of interest concerns the scaling of the adult dose and schedule of an agent to children without the benefit of any pediatric dosing data, as would be the case for a new drug approved for adults but not yet examined in pediatric clinical trials. Such a need was noted in the

FIG 9 Measurements of total caspofungin concentrations for human and monkey after a single dose of caspofungin. Data shown were obtained from data reported previously (21, 25). Expanded units for the vertical axis are $\mu\text{g/ml}$ per mg/kg .

introduction, both for guidance in off-label pediatric treatment and for planning purposes for eventual clinical trials. As described above, the application of the theory in scaling the dose and schedule from adults to children requires a knowledge of the ratio of fractions of the free drug dose, U_P/U_A , for toddler, child, and adolescent and knowledge of the variation of the ratio of circulation numbers, N_P/N_A , with body mass. The former ratios can be evaluated from *in vitro* measurements of free concentration fractions, as discussed above and as also needed for accurate determinations of MIC values of new agents (22). The latter ratios can be evaluated by using data from preclinical trials involving laboratory animals (4).

Details of the latter matter can be illustrated by using results reported previously by Sandhu et al. (21) for caspofungin and deal, in particular, with its disposition in monkeys (generally recognized as excellent models for humans). Concentration measurements provided an average β -phase half-life of 5.5 h for an average body mass of 4 kg. When used with previously reported data for the adult human (half-life of 11.4 h for a body mass of 70 kg), calculations indicate (for a power law description) that the half-life varies with body mass raised to the power of 0.25, in agreement with that found for the pediatric and adult data, as described above. Thus, the ratio of circulation numbers N_P/N_A is indicated by equation 12 to be independent of body mass, consistent with previous work.

For verification of these results, the scaling of concentration (single-dose) data can be considered, as indicated in Fig. 9. It can be seen that the measurements from the monkey and the scaled predictions from the adult human data are in excellent agreement with one another. The scaling relations used were those of equations 9 and 10, with the subscripts P and A now referring to monkey and human, respectively. The ratio of circulation numbers was chosen as $N_P/N_A = 1$, consistent with the above-described work with half-life values. Here, also, the tentative assumption was made that the ratio U_P/U_A equals 1.0 for free drug fractions, as found in previous work with children and adults, and the adequacy of this assumption is supported by the agreement shown.

Dosage and clearance. A final matter of interest is the connection

between drug dosage and clearance, as revealed by the present scaling description. Here, it will be convenient to restrict attention to the case where the free dose fractions, U , are the same for children and adults. Equation 14 then shows that clearance is expressible as follows:

$$\text{CL} \propto N^{-2} M^{2/3} \quad (28)$$

For the present purposes, the clearance is also assumed to be expressible by the general allometric relation

$$\text{CL} \propto M^b \quad (29)$$

with the exponent b denoting a constant dependent on the particular agent considered, as discussed in detail previously by Mahmood (14–16). Equations 28 and 29 then allow the circulation number, N , to be expressed as follows:

$$N \propto M^{1/3 - b/2} \quad (30)$$

Upon using the latter equations with equations 16 to 20, it can thus be seen that the scaling equations for dose rate, dosing interval, and dose per interval are expressible, in terms of body mass, M , and agent-dependent exponent b , as follows:

$$\frac{D_P^R}{D_A^R} = \left(\frac{M_P}{M_A} \right)^{b-1} \quad (31)$$

$$\frac{\Delta t_P}{\Delta t_A} = \left(\frac{M_P}{M_A} \right)^{7/12 - b/2} \quad (32)$$

$$\frac{\Delta D_P}{\Delta D_A} = \left(\frac{M_P}{M_A} \right)^{b/2 - 5/12} \quad (33)$$

An example of the use of these last equations is provided by the agent linezolid, where best-fit analyses of the clearance data for child, adolescent, and adult (given in Table 1) indicate clearance, CL , to be proportional to body mass, M , to the power b of 0.37. For the known condition that U_P equals U_A for this agent and for the values for the adult of an M_A of 70 kg, a Δt_A of 12 h, and a ΔD_A of 8.6 mg/kg, equations 31 to 33 then provide values for the child of a Δt_P of 7.3 h and a ΔD_P of 11.5 mg/kg, in agreement with the values given above (Table 2).

Appendix

Detailed development of scaling equations. (i) Drug concentration. The basic relation governing the present work is that shown by equation 3, as described in the text. After the substitution of $M^{1/12}$ for QT_B/M , this relation can be written as follows:

$$\frac{C}{UD} \frac{M^{-1/12}}{N} \propto f\left(\frac{t}{NT_B}\right) \quad (A1)$$

The scaling laws for concentration, given by equations 4 and 5, follow from fundamental reasoning with this relation. In particular, if the variable t/NT_B is held constant under a change in size, then the left-hand side will also be constant so that

$$\frac{C}{UD} \frac{M^{-1/12}}{N} = \text{constant when } \frac{t}{NT_B} = \text{constant} \quad (A2)$$

Upon evaluating the constants with values for the adult (denoted with a subscript A) and rearrangement, the following equations provide scaled results for children (denoted with a subscript P):

$$\left(\frac{C}{D}\right)_P = \frac{U_P}{U_A} \frac{N_P}{N_A} \left(\frac{M_P}{M_A}\right)^{1/12} \left(\frac{C}{D}\right)_A \quad (A3)$$

$$t_P = \frac{N_P}{N_A} \left(\frac{M_P}{M_A}\right)^{1/4} t_A \quad (A4)$$

which are the same as equations 4 and 5.

Equations 9 and 10 for the total concentration are established in the same way, after writing equation 8 as follows:

$$\frac{UC_T M^{-1/12}}{D N} \propto f\left(\frac{t}{NT_B}\right) \quad (\text{A5})$$

(ii) **Drug dose.** The restriction on the dose, D , so that the free concentration, C , is a function only of $f(t/NT_B)$ can be seen from equation A1 to require

$$UDNM^{1/12} = \text{constant} \quad (\text{A6})$$

Evaluating the constant with adult values, it is then found (with $D = M_D/M$) that

$$\left(\frac{M_D}{M}\right)_p = \frac{U_A N_A}{U_p N_p} \left(\frac{M_A}{M_p}\right)^{1/12} \left(\frac{M_D}{M}\right)_A \quad (\text{A7})$$

Assuming a body surface area, S , proportional to $M^{2/3}$ (as discussed below), this last equation can also be written as follows:

$$\left(\frac{M_D}{S}\right)_p = \frac{U_A N_A}{U_p N_p} \left(\frac{M_p}{M_A}\right)^{1/4} \left(\frac{M_D}{S}\right)_A \quad (\text{A8})$$

The latter two equations are the same as equations 6 and 7.

(iii) **PK variables.** Regarding scaling equations 12 to 14 for the PK variables associated with the total concentration, the equation for the half-life follows from equation A4, since any specific time, T , associated with the free or total drug concentration must scale as

$$T_p = \frac{N_p}{N_A} \left(\frac{M_p}{M_A}\right)^{1/4} T_A^* \quad (\text{A9})$$

which is the same as equation 12.

The scaling law for the volume of distribution, V , follows from its definition as the ratio of the dose M_D to the extrapolated initial concentration value of the beta phase, say, C_{TB} , that is,

$$V = DM/C_{TB} \propto DM/U^{-1}DNM^{1/12}f(0) \quad (\text{A10})$$

or

$$VNU^{-1}M^{-1/12} = \text{constant} \quad (\text{A11})$$

Evaluating the constant as described above, the following equation results:

$$V_p = \frac{U_p N_A}{U_A N_p} \left(\frac{M_p}{M_A}\right)^{11/12} V_A \quad (\text{A12})$$

which is the same as equation 13.

The equation for clearance involves the ratio of the drug volume, V , to time, T , and is expressible as follows:

$$CL \propto \frac{\text{volume}}{\text{time}} \propto \frac{V}{T} \quad (\text{A13})$$

Using equations A9 and A12, the scaling relation for clearance is thus found as

$$CL_p = \frac{U_p}{U_A} \left(\frac{N_A}{N_p}\right)^2 \left(\frac{M_p}{M_A}\right)^{2/3} CL_A \quad (\text{A14})$$

which is the same as equation 14.

Equations 15 through 23 for multiple dosing are derived in a similar manner.

Relation for body surface area. For mathematical simplification and manipulation, the variation of body surface area, S , with body mass, M , is represented in the present work by the power law relation

$$S = 0.108 M^{2/3} \quad (\text{A15})$$

with S in units of m^2 and M in units of kg. Results from this equation are shown in Fig. A1. Results are also shown from the formulas described previously by Boyd (2) and Mosteller (19), as described by Sharkey et al. (23). The Boyd formula (as used here) involves body

FIG A1 Illustration of the power law equation of the present work for describing body surface area and comparison with results from the Boyd (2) and Mosteller (19) descriptions.

mass only, and the Mosteller formula involves both body mass and height. The results shown in Fig. A1 from the Mosteller formula are for the case where body height is chosen as the 50th percentile value for a given body mass, as found from standard growth curves. The value of the coefficient (0.108) in equation A15 is chosen for a best-fit description of the Boyd and Mosteller relations.

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