RESEARCH ARTICLE

Pharmacokinetic scaling of epirubicin using allometric and species-invariant time methods

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Abstract The pharmacokinetics of epirubicin, an anthracycline, were investigated after intravenous bolus administration (5 mg/kg) in mice, rats, rabbits and dogs. Based on animal data, we predicted the following human pharmacokinetic parameters using allometric scaling: 120 and 35.2 L/h for total body clearance (CL_t) using simple and maximum life-span potential (MLP)-corrected allometry, respectively; 702 L for steady-state volume of distribution (V_{dss}). The scaled V_{dss} value was twofold lower than the corresponding values in humans. However, the scaled CL_t values were consistent with those clinically observed in humans (35.6–133.4 L/h). We also predicted human parameters using species-invariant time transformations (equivalent time, kallynochrons, apolysichrons and dienetichrons). The mean V_{dss} (854 L) obtained using kallynochrons and that derived from simple allometry were comparable. The lowest CL_t (121 L/h) derived using kallynochrons was comparable to that obtained using simple allometry. The results of this study also indicated that the predicted human CL_t generated using MLP-corrected allometry can be used for the selection of a safe dose for studies in healthy adult human volunteers. These results suggest that such approaches may be useful in designing pharmacokinetic studies for novel anthracyclines.

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Introduction

Anthracycline antibiotics such as epirubicin, daunorubicin, doxorubicin and idarubicin are clinically and commercially important anticancer agents. Epirubicin has activity similar to doxorubicin (Adriamycin) against a variety of solid neoplasms and haematological malignancies (Robert 1994). Epirubicin is more lipophilic than doxorubicin and has a larger volume of distribution (Ganzina 1983). Plasma levels of the compound after intravenous (i.v.) bolus administration were rapidly disappeared from the blood circulation with a terminal half-life of 20 h, longer than that of doxorubicin (Hu et al. 1989; Robert and Bui 1992; Robert and Gianni 1993; Robert 1994). Epirubicin is extensively distributed into tissues, and the elimination of the drug is mainly biliary (Robert 1994; Shin et al. 2013). The glucuronides of epirubicin and epirubicinol are important metabolites of the drug. This metabolic pathway, which is unique to epirubicin, might explain the better tolerability of this drug compared with that for doxorubicin (Robert 1994). Recently, we reported that epirubicin is taken into liver cells via organic anion transporting polypeptides, and that its biliary excretion may be mediated via specific transporters in rats (Shin et al. 2013, 2014).

The anthracycline antibiotics derived from *Streptomyces* have been one of the most prevalent classes of anticancer agents in the treatment of cancer patients (Robert 1994). However, because of its cumulative and dose-related cardiomyopathy (Von Hoff et al. 1982), the application of these antibiotics has been inhibited. Recently, a less toxic

analogue of anthracycline antibiotics, 11-hydroxyaclacino-mycin (hyrubicin), is being investigated in pre-clinical trials by a number of pharmaceutical companies (Lee et al. 2007; Ryu et al. 2006; Shin et al. 2008; Yoo et al. 2005a, b). The pharmacokinetic characteristics of epirubicin are widely known in both animals and humans. However, the extrapolation of animal data to predict pharmacokinetic parameters of epirubicin in humans would be highly useful information to have during this drug's development. Consequently, we investigated interspecies pharmacokinetic scaling approaches using epirubicin as a model anthracycline for the prediction of pharmacokinetic parameters in humans.

In the present study, the pharmacokinetic parameters of epirubicin were evaluated following i.v. bolus administration to four animal species, namely, mice, rats, rabbits and beagle dogs. The total body clearance (CL_t) in the animals was scaled using both simple and maximum life-span potential (MLP)-corrected allometry to predict the corresponding human value. The steady-state volume of distribution (V_{dss}) was also scaled using simple allometry. In addition, the pharmacokinetic parameters were predicted for a 70 kg human using species-invariant time transformation methods with data derived from these four species.

Materials and methods

Chemicals and reagents

Epirubicin was obtained from Boryung Pharmaceutical Co. Ltd. (Seoul, Korea). The solvents used in the epirubicin analysis were HPLC grade and were filtered and degassed just prior to use. All other chemicals were analytical reagent grade.

Animals

Male ICR mice (24–26 g), Sprague–Dawley rats (230–250 g), New Zealand white rabbits (2.3–2.5 kg) and beagle dogs (13–15 kg) were obtained from Sam Tac Co. Ltd. (Suwon, Gyeonggi-do, Korea). The animals were housed in plastic cages with wire tops and sawdust bedding, and were maintained in a controlled environment with a constant temperature (25 °C), 50 % relative humidity, and 12 h light/dark cycle. The animals were fed a low-fat diet for long-term breeding and had free access to water. The experimental and surgical protocols were approved by the Chungbuk National University Animal Welfare Committee.

HPLC analysis of epirubicin

To analyze epirubicin levels in the plasma samples, we used a reverse phase high-performance liquid chromatography (HPLC)-based method which has been validated in our laboratory (Shin et al. 2013). The mean regression equations for mouse, rabbit and dog were not significantly different from that for the rat.

Animal studies

Epirubicin (5 mg/kg) was administered as a single i.v. bolus to mice via the tail vein. Blood samples were taken at 1, 2, 5, 15, 30, 60, 120, 240 and 480 min after administration. Epirubicin (5 mg/kg) was administered to rats via a femoral vein, and blood samples were collected from the femoral artery. The rabbits were given a single i.v. bolus of epirubicin (5 mg/kg) administered into the left marginal ear vein, and blood samples were collected from the right marginal vein. The beagle dogs received epirubicin (5 mg/kg) as a single i.v. bolus administered into the left tarsal vein, and blood samples were taken from the right lateral tarsal vein. Blood samples of rats, rabbits and dogs were taken at the same times after administration as those for mice.

Pharmacokinetic analysis

Epirubicin plasma concentration profiles after i.v. bolus administration were analysed using a non-compartmental model with the nonlinear least-squares method (MULTI) (Yamaoka et al. 1981). The pharmacokinetic parameters were subsequently calculated as follows: the area under the plasma concentration–time curve from time zero to infinity (AUC) was calculated from the equation $AUC = AUC_t + C_t/k_{el}$, where C_t is the last quantifiable concentration and k_{el} is the elimination rate constant. The k_{el} was determined by linear regression of the terminal log-linear phase of the concentration–time curve. The area under the plasma concentration–time curve from time zero to the time of the last quantifiable concentration (AUC_t) was calculated using the linear trapezoidal rule approximation. The following parameters were also calculated using standard methods: $CL_t = Dose/AUC$, $Vd_{ss} = CL_t \cdot MRT$, the mean residence time (MRT) = AUMC/AUC, where AUMC represents the area under the first moment of the concentration–time curve.

Allometric scaling

The allometric approach is based on the power function, with the body weight from several different species plotted against the pharmacokinetic parameter of interest on a log–log scale (Mahmood 2007). The power function is written as follows:

$$Y = aW^b \tag{1}$$

where Y is the parameter of interest (CL_t or V_{dss}), W is the body weight (kg), and a and b are the coefficient and

exponent of the allometric equation, respectively. The exponent (b) is calculated from the slope of the regression line when plotted on log–log coordinates as follows:

$$log\ Y\ =\ log\ a\ +\ b\ log\ W \tag{2}$$

Studies indicate that CL_t of the drug cannot always be accurately predicted by relying on the use of Eq. 1 only (Mahmood and Balian 1996; Mahmood 2007). Thus, several different approaches have been put forward to improve the predictive capabilities of allometry for CL_t. One approach is based on neoteny, where CL_t is predicted from different species' body weights and MLPs (Mahmood 2007).

$$CL_t\ \times\ MLP\ =\ aW^b \tag{3}$$

where $8.18\ \times\ 10^5$ is the MLP value, in hours in humans. MLP in years was calculated from the following equation as described by Mahmood (2007):

$$MLP\ (years)\ =\ 185.4(BrW)^{0.636}(W)^{-0.225} \tag{4}$$

where BrW and W represent brain weight (kg) and body weight (kg), respectively.

Species-invariant time methods

Other approaches to allometric scaling use the species-invariant time methods (Boxenbaum 1982, 1984; Boxenbaum and Ronfeld 1983; Dedrick et al. 1970; Mahmood and Balian 1996; Shin et al. 2003). Chronological time, known as species-invariant time, is transformed into physiological time using the following equations.

The equivalent time model is expressed as:

$$Y-axis\ =\ Concentration\ /\ (Dose/W) \tag{5}$$

$$X-axis\ =\ Time\ /\ W^{0.25} \tag{6}$$

The elementary Dedrick plot (kallynochrons) is expressed as:

$$Y-axis\ =\ Concentration\ /\ (Dose/W) \tag{7}$$

$$X-axis\ =\ Time\ /\ W^{1-x} \tag{8}$$

where x is the exponent of clearance.

The complex Dedrick plot (apolysichrons) is expressed as:

$$Y-axis\ =\ Concentration\ /\ (Dose/W^y) \tag{9}$$

$$X-axis\ =\ Time\ /\ W^{y-x} \tag{10}$$

where x and y are exponents of clearance and volume of distribution, respectively.

The plot using dienetichrons is expressed as:

$$Y-axis\ =\ Concentration\ /(Dose/W^y) \tag{11}$$

$$X-axis\ =\ Time\ /\ \left(MLP\ \times\ W^{1-x}\right) \tag{12}$$

where x is the exponent of clearance.

The equivalent time model, kallynochrons, apolysichrons and dienetichrons were all used in the present study to determine whether epirubicin could be scaled in mice, rats, rabbits, dogs and humans. The scaled concentration–time curves were fitted to calculate the pharmacokinetic parameters in humans using the nonlinear least-squares method (MULTI) (Yamaoka et al. 1981) as described above. The superimpositions of the concentration–time curves obtained from different animal species for respective pharmacokinetic time units were evaluated with the coefficient of variation (r^2).

Results

Pharmacokinetics

The plasma concentration versus time profiles of epirubicin in mice, rats, rabbits and dogs following i.v. bolus administration (5 mg/kg) are presented in Fig. 1. The pharmacokinetic parameters are summarized in Table 1. The dog showed the highest dose-normalized AUC, which was fourfold greater than that for the mouse and rat, both of which, by approximation, showed the lowest AUC values. The mean estimated CL_t increased across species, from 0.17 L/h in the mouse to 28.8 L/h for the dog. The lowest mean V_{dss} (0.454 L) was observed for the mouse and for the dog, with the highest estimate at 101.2 L.

Allometric scaling

Table 2 shows the allometric equations and the coefficients derived from linear regression analysis of the log-transformed animal CL_t or V_{dss} versus the corresponding log-transformed animal body weight, as presented in Fig. 2. The regression analysis showed strong correlations based on the coefficients of determination (r-squared values) for CL_t (0.997 and 0.999 for the simple and MLP-corrected allometry, respectively) and for V_{dss} (0.988 for simple allometry). The allometric exponents derived from the simple allometry were 0.812 for CL_t, 0.929 for V_{dss}, and that derived from the MLP-corrected allometry for CL_t was 1.11.

Table 2 shows scaled CL_t estimates of 120 L/h and 35.2 L/h for a 70 kg human using simple and MLP-corrected allometry, respectively, and a scaled V_{dss} estimate of 702 L for a 70 kg human using simple allometry. The estimated CL_t values were comparable to those clinically derived in humans (35.6–133.4 L/h) (Camaggi et al. 1988, 1993; Ganzina 1983; Robert and Gianni 1993; Robert 1994).

Table 1 Pharmacokinetic parameters of epirubicin after an i.v. bolus (5 mg/kg) administered to mice, rats, rabbits and dogs

Parameter	Mouse	Rat	Rabbit	Dog
Brain weight [a] (BrW, g)	0.36	1.80	14.0	80.0
Body weight (W, kg)	0.0251 ± 0.0021	0.248 ± 0.005	2.47 ± 0.09	14.5 ± 0.1
CL_t (L/h)	0.166 ± 0.029	1.46 ± 0.36	8.96 ± 0.59	28.8 ± 10.6
V_{dss} (L)	0.454 ± 0.131	2.16 ± 0.66	36.1 ± 3.3	101.2 ± 26.0
AUC (µg h/L)	773 ± 156	870 ± 116	1383 ± 95	2941 ± 1313

Each value represents the mean $\pm$ SD of three different experiments

[a] From Davies and Morris (1993)
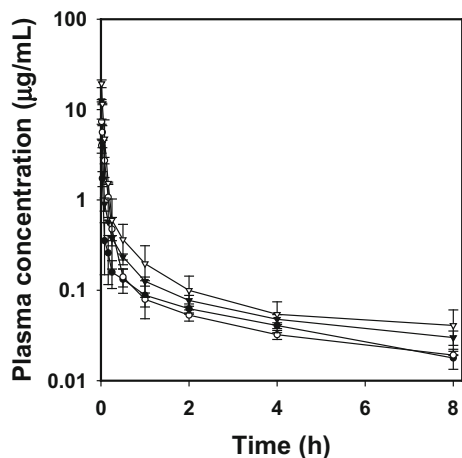
Fig. 1 The plasma concentration–time profiles of epirubicin following an i.v. bolus (5 mg/kg) administered to mice (*filled circle*), rats (*open circle*), rabbits (*filled inverted triangle*) and dogs (*open inverted triangle*). Each point represents the mean $\pm$ SD of three different experiments

Species-invariant time models

The plasma concentration–time data obtained in these four species were further normalized using the pharmacokinetic times of equivalent time, kallynochrons (elementary Dedrick plot), apolysichrons (complex Dedrick plot) and dienetichrons. The concentration–time curves for epirubicin predicted in humans after an i.v. injection (5 mg/kg) using these pharmacokinetic time methods are shown in

Fig. 3. Table 3 shows the values for the pharmacokinetic parameters of AUC, V_{dss} and CL_t predicted for a 70 kg human based on these species-invariant time methods. The lowest mean V_{dss} (368 L) was observed using equivalent time and the highest estimate (845 L) using kallynochrons. The mean V_{dss} obtained using kallynochrons was comparable to that obtained using simple allometry (702 L) (Table 2). The lowest CL_t (121 L/h) predicted using kallynochrons was comparable to that obtained using simple allometry (120 L/h), but that value was approximately twofold lower than those generated using apolysichrons or dienetichrons (Table 3).

Discussions

Anthracyclines are clinically important anticancer agents. Recently, a less toxic analogue of anthracycline antibiotics is being investigated in pre-clinical trials; thus, the extrapolation of pharmacokinetic parameters of epirubicin, an analogue of anthracycline antibiotics, from animals to humans would provide valuable information during the development of these drugs. Interspecies scaling is one approach that can be used to estimate the safe dose for phase I studies. In the present study, the pharmacokinetic parameters of epirubicin were evaluated following i.v. bolus administration to four animal species, namely, mice, rabbits, rats and beagle dogs. The human values for the CL_t

Table 2 Allometric equations, coefficients and scaled human pharmacokinetic parameters for a 70 kg human generated using simple or MLP-corrected allometry based on data from mice, rats, rabbits and dogs

Parameter	Allometric equation	Coefficient (r^2)[a]	Scaled human value
CL_t (L/h)	$y = 3.82\ W^{0.812}$	0.997	120[b]
CL_t (L/h)	$y = 29.6\ W^{1.11}$	0.999	35.2[c]
V_{dss} (L)	$y = 11.4\ W^{0.929}$	0.988	702[b]

[a] Values from linear regression analysis of the parameter–body weight plots on a log–log scale (Fig. 2)

[b] Values from simple allometry

[c] Value from MLP-corrected allometry. The CL_t of 35.2 L/h was calculated as the human $CL_t \cdot$ MLP (L·year/h) divided by the human maximum life-span potential (MLP) of 93.4 years (Mahmood 2007)

Fig. 2 Log-transformed parameters of V_{dss} (**a**), CL_t (**b**), $CL_t \times MLP$ (**c**) versus log-transformed corresponding animal body weights of mice (*filled circle*), rats (*open circle*), rabbits (*filled inverted triangle*) and dogs (*open inverted triangle*) following an i.v. bolus of epirubicin (5 mg/kg) administered to the animals. Each point was plotted using the mean value of V_{dss} and CL_t (Table 1). The human pharmacokinetic parameters were predicted using linear regression analysis
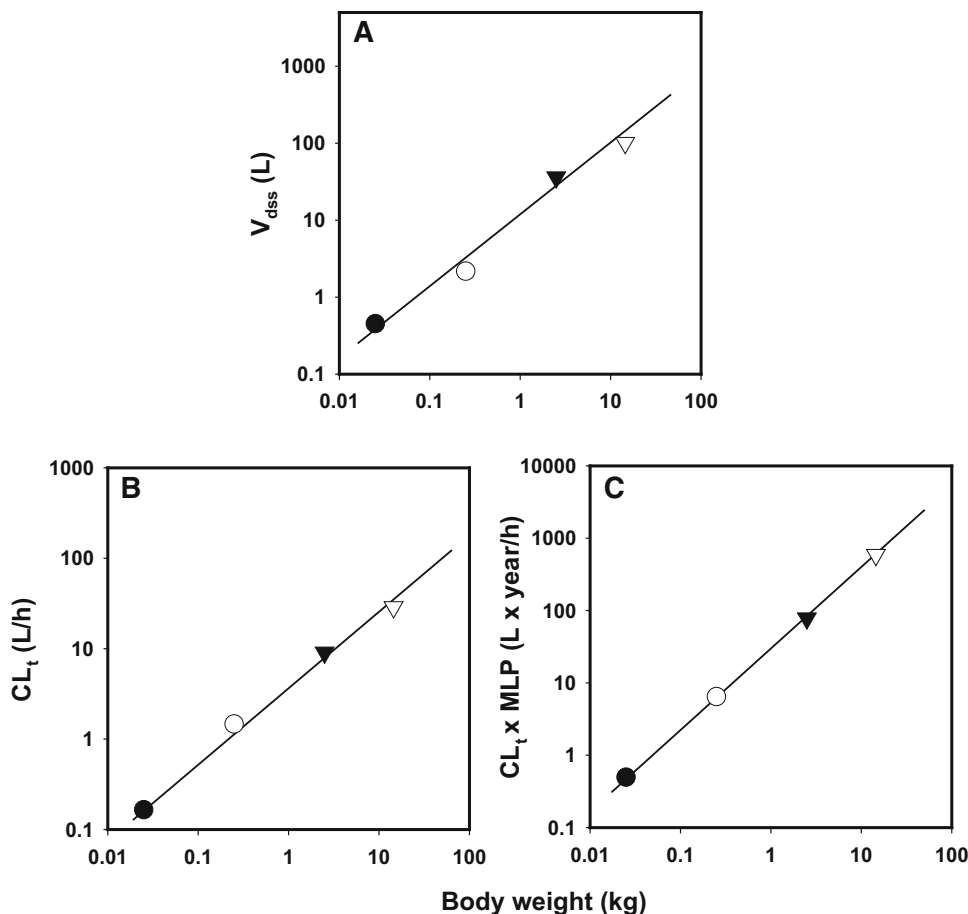
Table 3 Scaled pharmacokinetic parameters for a 70 kg human based on species-invariant time methods

| Parameter	Equivalent time	Kallynochrons	Apolysichrons	Dienetichrons
AUC (μg·h/L)	2651	2901	1428	1417
CL_t (L/h)	132	121	245	247
V_{dss} (L)	368	845	384	393
r^2	0.948	0.954	0.797	0.831

The plasma concentration–time curves of four animal species (Fig. 3) were normalized based on the time transformations. The parameters for a 70 kg human were calculated from the curves using non-compartmental analysis

and V_{dss} of epirubicin were scaled using allometry and four species-invariant time methods.

Mahmood (2007) reported that three or more preclinical species are adequate for reliable scaling of CL_t using allometry. The present study used four species to scale CL_t and V_{dss} to determine estimates of those parameters in humans. Based on the exponents of simple allometry, it was previously determined that three methods can be used for reasonably accurate predictions of clearance (Mahmood 2007). The following conclusions were drawn from their studies. If the exponent of the simple allometry is within 0.55–0.70, simple allometry will predict clearance accurately; if the exponent of the simple allometry lies between 0.71 and 0.99, the $CL_t \times MLP$-corrected allometry is

applied; and if the exponent of the simple allometry is greater than 1.0, then the $CL_t \times$ brain weight (BrW)-corrected allometry is suitable. Mahmood (2007) termed their approach the rule of exponents (ROE). In the present study, the allometric exponent derived from simple allometry was 0.812 for CL_t (Table 2); therefore, BrW-corrected allometry was not used. The CL_t value in a 70 kg human was calculated to be 120 L/h and 35.2 L/h using simple and MLP-corrected allometry, respectively (Table 2). These estimated values were comparable to those clinically derived in humans (35.6–133.4 L/h) (Camaggi et al. 1988, 1993; Ganzina 1983; Robert and Gianni 1993; Robert 1994). The CL_t of 121 L/h predicted using kallynochrons was nearly identical to that obtained with simple allometry

Fig. 3 The plasma
concentration–time values after
time transformations of the data
from mice (*filled circle*), rats
(*open circle*), rabbits (*filled
inverted triangle*) and dogs
(*open inverted triangle*). Each
point was calculated from the
mean value for each animal data
(Fig. 1). The *Y*- and *X*-axes
were transformed based on
equivalent time (**a**),
kallynochrons (**b**),
apolysichrons (**c**) and
dienechrons (**d**) where x and y is
the exponent of clearance and
volume of distribution,
respectively. The units of
concentration, time, dose, body
weight (W) and MLP are µg/
mL, h, mg/kg, kg and years,
respectively. The solid lines
were fitted to the values
obtained from the animal data
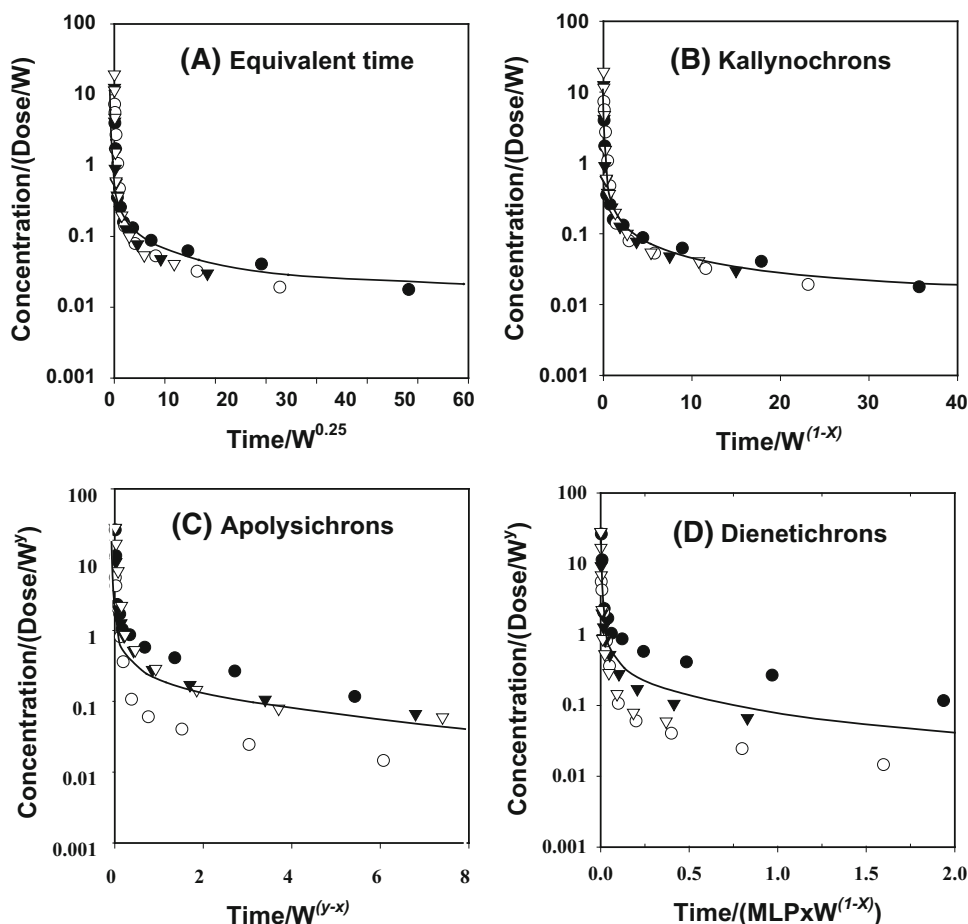
(120 L/h) (Table 3). However, the estimated CL_t values
derived from the apolysichrons or dienetichrons were
approximately twofold larger than that generated using
kallynochrons (Table 3).

There was a good correlation ($r^2 = 0.988$) between
body weight and V_{dss} in the four animal species (Table 2).
Generally, the exponents of volume do not vary as widely
as those of clearance and are approximately 0.8–1.10
(Mahmood 2007). In the present study, the allometric
exponent derived from a simple analysis was 0.929 for V_{dss}
(Table 2). The scaled V_{dss} value of 702 L obtained using
simple allometry was approximately twofold lower than
the clinical values (1000–1500 L/70 kg) (Camaggi et al.
1988; Robert 1994). In addition, the estimated V_{dss} value
(854 L) generated using kallynochrons was comparable to
the value obtained using simple allometry (702 L)
(Table 3). It is reported that epirubicin is more lipophilic
than doxorubicin and has a higher volume of distribution
compared with the other anthracyclines (Robert and Gianni
1993; Robert 1994). The higher lipophilicity of epirubicin
may be one reason for the poor correlation between V_{dss}
and the physiological function of the body weight. How-
ever, Mahmood (2007) suggested that the scaled V_{dss} value

may be less relevant than the scaled CL_t value for deter-
mining the first-in-human (FIH) dose.

Unlike clearance and volume of distribution, the corre-
lation between body weight and half-life has generally
been found to be poor, and the exponents of half-life vary
widely (Mahmood 2007). In the present study, it was dif-
ficult to establish a relationship between body weight and
half-life (data was not shown). This may be due to the fact
that half-life is not directly related to the physiological
function of the body rather it is a hybrid parameter
(Mahmood 2007; Shin et al. 2003). As a result, these
approaches for $t_{1/2}$ scaling cannot be used for dose titration
studies in phase I clinical trials of epirubicin.

The estimation of a starting FIH dose for clinical trials
of anticancer drugs in healthy volunteers is very important
because anticancer drugs may not be given to healthy
subjects. Generally one tenth of the LD_{10} in mice or one-
third of the toxic dose level (TLD) in the dog in milligrams
per square meter is used as the starting dose in phase I
clinical trials (Reigner and Blesch 2002). However, it is not
clear as to why dosing by body surface area (BSA) was
extended to the routine dosing of antineoplastic agents
(Sawyer and Ratain 2001). They demonstrated that

epirubicin was found to have no significant relationships between the pharmacokinetics and BSA. Thus, we used the lowest AUC at the no-observed-adverse-effect-level (NOAEL) for epirubicin given to four species as well as the use of the predicted human clearance (Dose in humans = AUC in animal x predicted human clearance). For this approach, it is essential that the dose given to animals is much lower than the NOAEL. Bertazzoli et al. (1985) reported that the LD_{50} of epirubicin was 16.7 mg/kg in mice, 14.3 mg/kg in rats. Thus, in the present study, the scaled CL_t value of 35.2 L/h derived from MLP-corrected allometry and the lowest animal AUC value were used to estimate the starting dose in healthy volunteers. As a result, the calculated FIH dose of 28.9 mg/70 kg was in reasonable agreement with the doses given in phase I clinical studies (18–36 mg/1.9 m^2) (Kimura et al. 1984; Snyder et al. 1987). The maximum tolerated dose (MTD) of epirubicin was first established to be approximately 152 mg/1.9 m^2, although this was recently re-calculated to be approximately 285 mg/1.9 m^2 in humans, which is about twofold higher than the MTD of doxorubicin (Kimura et al. 1984; Robert and Gianni 1993). Epirubicin is widely used in patients for chemotherapy at a dose of 114 mg/1.9 m^2 (60 mg/m^2) (Camaggi et al. 1988, 1993; Kimura et al. 1984). The estimated human dose of 98.6 mg/70 kg derived from simple allometry using the CL_t (120 L/h) and the lowest animal AUC value was comparable with to the clinical dose of 114 mg/1.9 m^2 used in chemotherapy. These doses were also in reasonable agreement with the human dose predicted from the CL_t (121 L/h) using kallynochrons. These approaches however, are not perfect because epirubicin may not be given to healthy subjects.

In conclusion, the pharmacokinetic disposition of epirubicin was studied after an i.v. bolus injection in mice, rats, rabbits and dogs. The scaled V_{dss} value derived using simple allometry was approximately twofold lower than that clinically observed in humans. However, the scaled CL_t values generated with allometry and kallynochrons closely approximated the corresponding clinically observed values. The results of this study also indicated that the predicted human CL_t generated using MLP-corrected allometry can be used for the selection of a safe dose for studies in healthy adult human volunteers. These results suggest that allometric and species-invariant time approaches may be useful in designing early pharmacokinetic studies examining novel anthracyclines.

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