Cancer Chemother Pharmacol (2003) 51: 395–402
DOI 10.1007/s00280-002-0554-z

ORIGINAL ARTICLE

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The effect of age on the early disposition of doxorubicin

Received: 6 June 2002 / Accepted: 18 October 2002 / Published online: 1 April 2003

Abstract *Purpose*: Clinical studies indicate that anthracycline cardiotoxicity increases with patient age. This may be due to altered pharmacokinetics or pharmacodynamics. A parameter termed 'early clearance' has been shown to decrease with age in patients receiving intravenous doxorubicin. This parameter, as defined, has no immediate relationship to any physiologically based pharmacokinetic parameter. We therefore reevaluated the pharmacokinetic data to better define the relationship between doxorubicin disposition and patient age. *Methods*: Four studies provided a total of 56 patients with evaluable pharmacokinetics. The volume of the central compartment, V_c, the distribution clearance, CL_d, and total body clearance, CL, were determined for each patient and regressed against age. A physiologically based pharmacokinetic (PBPK) model for doxorubicin was also used to evaluate the effects of age on doxorubicin disposition. Published blood flows associated with various patient ages were used to simulate plasma and tissue doxorubicin concentrations. The relationship between CL_d and initial tumor regression was also evaluated. *Results*: No correlation was found between V_c and age ($P > 0.05$). A highly significant correlation was observed between CL_d and age ($P < 0.0005$) and there was a mild but significant relationship between CL and age ($P < 0.01$). Use of the PBPK model with different age-related blood flows yielded virtually identical parameter values to the clinical data analyzed. Furthermore, relative tissue AUCs simulated in old and young patients compared well with those reported for daunorubicin disposition in young and old rats. In addition, a linear relationship was observed between initial tumor regression and CL_d. *Conclusions*: Initial concentrations of doxorubicin following intravenous administration are higher in the elderly due to a decrease in CL_d rather than in V_c. On the basis of simulations with the PBPK model, the reduced CL_d appears to be related to altered regional blood flows in the elderly, and such changes may be of clinical significance.

Keywords Age · Pharmacokinetics · Doxorubicin

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Introduction

Anthracyclines, including doxorubicin, are frequently used in the treatment of cancer. However, their use has been associated with the development of congestive heart failure [1]. This toxicity may occur as early as a year after the start of anthracycline treatment while in other patients it appears years, even decades, after drug administration [2]. Mortality associated with anthracycline treatment has been estimated to be as high as 60% [1, 2]. Certain factors appear to predispose patients to the drug-induced congestive heart failure including cumulative anthracycline dose, drug administration rate and patient age [1, 3, 4, 5]. If the last is associated with altered pharmacokinetics, a common mechanism for the life-threatening cardiotoxicity may involve anthracycline concentration-dependent toxicity.

Cusack et al. [6] have recently described the pharmacokinetics of daunorubicin in young and senescent rats following intravenous (i.v.) bolus injection. They report that drug concentrations at the earliest time points measured in the older animals were substantially higher than those found in younger rats. Higher daunorubicin concentrations in the heart were also found. These observations support altered anthracycline pharmacokinetics as a potential contributing factor to the increased cardiotoxicity in advanced age.

It appears that the pharmacokinetics of anthracyclines in elderly patients have not been directly studied. However, Robert et al. have reported several studies in which the pharmacokinetics of doxorubicin in patients of varying ages were examined [7, 8, 9, 10, 11]. Furthermore, they describe a significant relationship between a parameter they term 'early clearance' and patient age. However, the correspondence of this parameter to physiological processes is unclear. In view of the relationship between age and anthracycline-induced cardiotoxicity, we reevaluated the data of Robert et al. in terms of physiologically related pharmacokinetic parameters with the aim of providing a better understanding of the effect of age on doxorubicin disposition.

Material and methods

Patients

A retrospective analysis was performed on 56 cancer patients (Table 1) receiving i.v. doxorubicin by either short infusion over 3–6 min or bolus injection. None of the 56 patients had signs of renal or hepatic dysfunction [7, 8, 9, 10, 11]. Each patient received a doxorubicin dose of at least 30 mg/m^2. Although each patient was treated with combined chemotherapy, doxorubicin was the first dose administered. Other drugs were administered after completion of the doxorubicin pharmacokinetic sampling protocol. Patients with estimates of only early clearance but not total clearance were excluded from the study. This resulted in the exclusion of 6 out of 62 patients.

Pharmacokinetic analysis of the data

The original pharmacokinetic analysis was performed by Robert et al. using a three-compartment model to fit the observed doxorubicin plasma concentrations. For a short i.v. infusion [7], the equation used was:

$$C(t)=\frac{D}{T}\left[\frac{A_1'}{\lambda_1}\left(e^{\lambda_1 T}-1\right)e^{-\lambda_1 t}+\frac{A_2'}{\lambda_2}\left(e^{\lambda_2 T}-1\right)e^{-\lambda_2 t}+\frac{A_3'}{\lambda_3}\left(e^{\lambda_3 T}-1\right)e^{-\lambda_3 t}\right] \quad (1)$$

For i.v. bolus administration [8], the equation used was:

$$C(t)=A_1e^{-\lambda_1 t}+A_2e^{-\lambda_2 t}+A_3e^{-\lambda_3 t} \quad (2)$$

where D is doxorubicin dose injected, A_2, A_2' and λ_i are parameters of the compartment model and, in accordance with the terminology of Robert et al., $A_i'=A_i/D$. The parameter λ_1 corresponds to the initial log-linear slope, whereas A_1 and A_1' correspond to the intercept and the dose-normalized intercept of the drug concentration-time curve. The assumption made by the authors that $A_1>>A_2$ and A_3, and $\lambda_1>>\lambda_2$ and λ_3 was tested. The differences between A_1 and $\sum_{i=1}^{3}A_i$ and that between λ_1 and $\sum_{i=1}^{3}\lambda_i$ were less than 5%. Therefore, since $A_1>>A_2$ and A_3, and $\lambda_1>>\lambda_2$ and λ_3, the early decline in doxorubicin concentrations could be adequately described by Eqs. 3 and 4, so that for the short i.v. infusion [11], Eq. 1 is simplified to:

$$C(t)=\frac{D}{T}\frac{A_1'}{\lambda_1}\left(e^{\lambda_1 T}-1\right)e^{-\lambda_1 t} \quad (3)$$

and for the i.v. bolus [8], Eq. 2 is likewise simplified to:

$$C(t)=A_1e^{-\lambda_1 t} \quad (4)$$

Robert et al. define 'early clearance' (CL_e) by the following equations.

Table 1 Characteristics of patients ($n=56$)

Age(years)	
Median	50
Range	12–74
Sex(M/F)	28/28
Dose(mg/m^2)	
Median	50
Range	30–75
Tumor type (no. of patients)	
Breast carcinoma	17
Non-Hodgkin's lymphoma	9
Bronchogenic carcinoma	3
Tongue carcinoma	1
Sarcoma	26
Chemotherapy regimen received (no. of patients)	
Doxorubicin + vincristine + methtrexate	17
Doxorubicin + cyclophosphamide + vincristine + prednisone	9
Doxorubicin + cyclophosphamide + vincristine + DTIC	9
Doxorubicin + eldisine + cisplatinum	11
Doxorubicin + vincristine	3
Doxorubicin + cisplatinum	3
Concomitant medication not characterized	4

For the short i.v. infusion, Cl_e [10, 11] is expressed as:

$$CL_e=\frac{1}{\frac{A_1'}{\lambda_1}}$$

For the i.v. bolus [8], the parameter is:

$$CL_e=\frac{D}{\frac{A_1}{\lambda_1}}$$

When CL_e was plotted against patient age, a highly significant correlation was obtained ($r=-0.623$, $P<0.0005$) [10]. CL_e as defined, however, has no immediate relationship to primary pharmacokinetic disposition parameters, i.e. clearance or volume. We therefore reanalyzed the data from several studies reported by Robert and coworkers [7, 8, 9, 10, 11] in which this term was used. Changes in the initial decline of doxorubicin with patient age are most likely due to alterations in the apparent volume of the central compartment (V_c) and CL_d, the distribution clearance of drug from the central to tissue compartments.

Because Robert et al. reported pharmacokinetic parameters for individual patients, we were able to determine both V_c and CL_d for each patient using the following equations described by Veng-Pedersen [12] for i.v. bolus dose administration:

$$V_c=\frac{D}{C(0)} \quad (5)$$

$$CL_d=\frac{D\times[-C'(0)]}{C(0)^2}-CL \quad (6)$$

where $-C'(0)$ and $C(0)$ represent the slope of the initial decline in doxorubicin plasma concentrations and the estimated doxorubicin concentration at zero time, respectively.

For three-compartment model analysis following i.v. bolus administration, $-C'(0)=\sum_{i=1}^{3}A_i\lambda_i$ [12] which in the case of doxorubicin can be reduced to $A_1\lambda_1$ according to the assumptions cited above. Furthermore, $C(0)=\sum_{i=1}^{3}A_i$ [12], which again for doxorubicin C(0) can be simplified to A_1. The calculation of C(0) in the case of infusion was modified as recommended by Gibaldi and Perrier [13], that is $C(0)=D\times A_1'\frac{1-e^{-\lambda_1 T}}{\lambda_1 T}$ where T is the duration of the infusion. The other parameters were the same as described above.

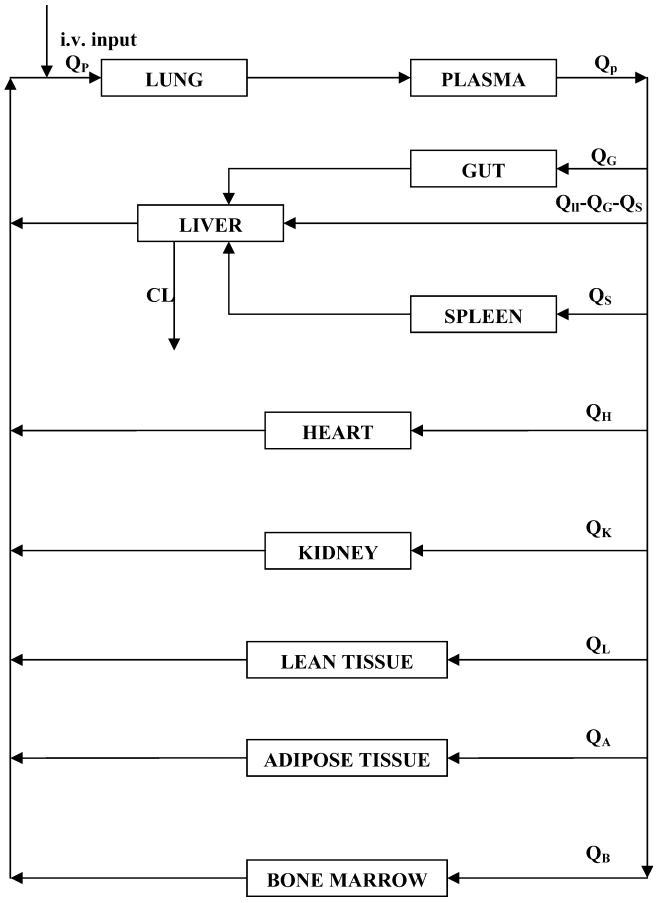

Fig. 1 Schematic diagram of the physiologically based pharmacokinetic model for doxorubicin

Parameters from the three-compartment model for doxorubicin were incorporated into Eqs. 5 and 6 to yield V_c and CL_d for individual patients [7, 8, 9, 10, 11]. From reference 12:

$$\begin{aligned} V_c \frac{D}{C(0)} &= \frac{1}{A_1'}\left(\frac{\lambda_1 T}{1-e^{-\lambda_1 T}}\right) \quad \text{(i.v. infusion)} \\ V_c &= \frac{D}{A_1} \qquad\qquad \text{(i.v. bolus)} \end{aligned} \tag{7}$$

and

$$\begin{aligned} CL_d &= \frac{D\times\left(A_1'\frac{1-e^{-\lambda_1 T}}{\lambda_1 T}\times\lambda_1\times D\right)}{\left(D\times A_1'\frac{1-e^{-\lambda_1 T}}{\lambda_1 T}\right)^2} - CL \quad \text{(i.v. infusion)} \\ CL_d &= \frac{D\times(A_1\times\lambda_1)}{A_1^2} - CL \qquad\qquad \text{(i.v. bolus)} \end{aligned} \tag{8}$$

where $D \times A_1' \frac{1-e^{-\lambda_1 T}}{\lambda_1 T} = A_1$ and $A_1' \frac{1-e^{-\lambda_1 T}}{\lambda_1 T} \times \lambda_1 \times D = A_1 \times \lambda_1$, corresponding to C(0) and the slope of the early phase disposition of doxorubicin, respectively.

The pharmacokinetic parameters A_1, λ_1, CL and the dose (D) for each patient (or in some cases, the $t_{1/2}$ of the λ_1 phase) were all reported by Robert et al.

Development of a physiologically based pharmacokinetic (PBPK) model for doxorubicin in humans

To relate physiological changes with age to alterations in doxorubicin pharmacokinetics, it is beneficial to use a PBPK model (Fig. 1). This permits incorporation of age changes in regional blood flow and the resulting effects on the distribution and clearance of doxorubicin.

Table 2 Model parameters for doxorubicin PBPK model correspond to a 35-year-old 70-kg individual (from reference 11)

Organ/tissue	Plasma flow (ml/min)	Tissue volume (ml)	Partition coefficient
Plasma	3438	2,670	
Lungs	3438	600	155 ± 24
Liver	891	1,700	45 ± 8.3
Kidneys	605	1,060	512 ± 45
Heart	149	450	57 ± 5.0
Bone marrow	66	1,400	91 ± 13
Adipose tissue	231	7,980	19 ± 3.5
Lean tissue	501	38,250	29 ± 3.6
Gut	970	3,180	51 ± 7.7
Spleen	138	200	556 ± 46

Table 3 Tissue plasma flow in patients of different ages (from reference 12)

	35 years (standard values)	55 years	75 years	95 years
Organ/tissue flow (ml/min)				
Liver	891	748	606	463
Kidneys	605	460	315	169
Heart	149	133	117	104
Bone marrow	66	66	66	66
Adipose tissue	231	176	120	65
Lean tissue	501	448	395	351
Gut	534	449	363	278
Spleen	138	116	94	72
CL(l/h)	66.87	51.42	35.98	20.53

In order to fully evaluate the effect of age on doxorubicin pharmacokinetics, we combined components from two previously developed doxorubicin PBPK models by Harris and Gross [14] and Chan et al. [15]. Insufficient information regarding tissue binding in these models limited us to the use of the tissue/blood partition coefficient alone to describe doxorubicin tissue binding. Nevertheless, our model-predicted patient doxorubicin plasma concentration-time data agreed closely those described by the previous models. Thus, doxorubicin plasma concentrations generated by our modified PBPK model fell within ± 1 SD of the compartmental model fit of the patient data described by Chan et al. [15]. In all PBPK models, blood flow was transformed to plasma flow using a hematocrit value of 45%. Plasma flows and tissue volumes used corresponded to an individual of weight 70 kg (Table 2).

Age-dependent blood flows were obtained from yet another PBPK model developed by Wada et al. [16] who investigated the effects of age on thiopental kinetics. From this study, specific blood flows to kidney, heart, lean tissues, liver, gut, spleen and adipose tissues were reduced by 12%, 5%, 5%, 8%, 8%, 8%, 12% per decade, respectively, relative to a standard 35-year-old human. Inserting these age-related blood flows into the doxorubicin PBPK model permitted an evaluation of the effect of age on the disposition of doxorubicin.

One further refinement to the calculations of the effects of age on doxorubicin kinetics in the models described above was adjustment of age-related changes in total clearance. Using data reported by Robert et al. [7, 8, 9, 10, 11], doxorubicin clearance was found to decline with age. The relationship between doxorubicin clearance and age was characterized by a linear regression providing the equation $CL = 93.898 - 0.7723(\text{age})$. This relationship in turn was incorporated into the final doxorubicin PBPK model, so that the performance of the model would also reflect declining doxorubicin clearance with age. The plasma flow rate through each organ for the four age groups used in this PBPK model and the estimated total clearance are summarized in Table 3.

Simulations were performed with an i.v. bolus administration of 50 mg doxorubicin. Doxorubicin concentration-time profiles in plasma and tissues for subjects with different ages were simulated using the commercial software package Berkeley Madonna (University of California, Berkeley, Calif.) [17]. The equations used in the model are presented in the Appendix. The Runge-Kutta 4 algorithm was chosen for numerical integration.

Pharmacokinetic analysis

To relate the physiological changes with age to the pharmacokinetic observations of Robert et al., doxorubicin plasma concentration-time curves generated were equivalent to three different ages using the PBPK model. Compartment model fits of this simulated data were then compared with the compartmental analysis undertaken by Robert et al.

Noncompartment pharmacokinetic methods were used to calculate the mean residence time (MRT), apparent steady-state volume of distribution (V_{SS}), total body clearance (CL). MRT was determined as the ratio AUMC/AUC and CL was calculated from the ratio dose/AUC. V_{SS} was obtained from the product of CL and MRT. AUC was calculated with use of the linear trapezoidal rule evaluated to the last non-zero concentration and then extrapolated to infinity. The slope of the terminal portion of the concentration-time profile was determined by log-linear regression.

The compartmental parameters (A_i and λ_i) were obtained by fitting a three-compartment model with i.v bolus input and first-order elimination to the PBPK-simulated doxorubicin concentration-time profile for each age group by nonlinear regression using the WinNonlin software package (Scientific Consulting, Apex, N.C.).

Simple linear regression was used to relate the pharmacokinetic parameters (CL, Cl_e, V_c and CL_d) to patient age in order to evaluate the relationship between age and the pharmacokinetic parameters of doxorubicin. Statistical significance was accepted at $P < 0.05$ (two-tailed comparison).

Pharmacodynamic analysis

In a series of 12 patients with locally advanced breast cancer treated primarily with doxorubicin [7], linear regression was used to relate the reduction in tumor mass at 3 weeks to CL_d.

Results

We studied the correlation between patient age and the CL_e, CL, CL_d and V_c of doxorubicin. A strong correlation between age and early clearance ($P < 0.0005$) and a mild but significant correlation between age and total body clearance ($P < 0.01$; Fig. 2) were consistent with the findings of Robert et al. [10]. CL_d showed a strong correlation with age ($P < 0.0005$; Fig. 3), whereas no statistically significant relationship was observed between V_c and age ($P > 0.05$). CL_d is clearance of doxorubicin from the central compartment to the tissue compartments. We conclude that the relationship between the 'early clearance' and age reported by Robert et al. is due to a decrease in the distribution clearance (CL_d) of doxorubicin and not a decrease in V_c. A similar finding has been reported for thiopental [18].

Using the PBPK model, Fig. 4 shows the simulated doxorubicin concentration-time profile in plasma and heart tissue, demonstrating that age-related physiological

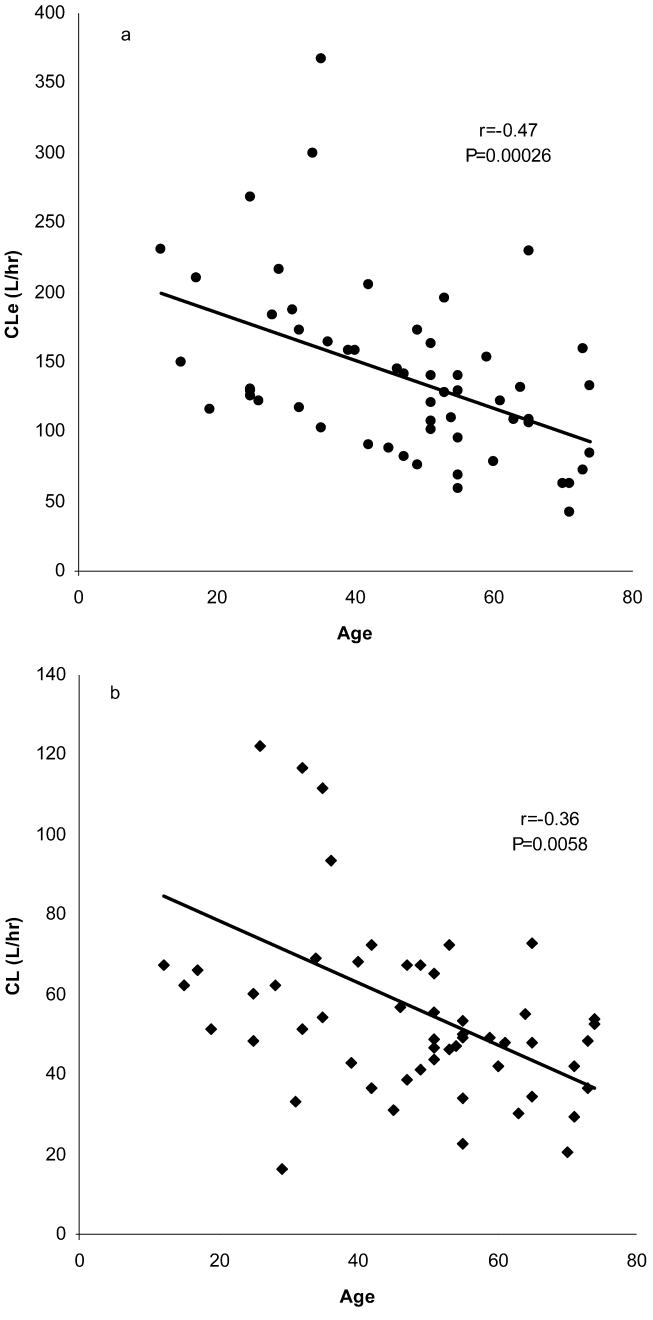

Fig. 2a, b Relationship between age and (**a**) the early clearance (CL_e) of doxorubicin and (**b**) total body clearance (CL). Significant correlations are evident ($r = -0.47$, $P = 0.00026$, and $r = -0.36$, $P = 0.0058$, respectively)

changes have a relatively minor effect on the estimated zero-time plasma concentration (from 661.26 to 658.63 ng/ml), but the rate constant (λ_1) of initial distribution in plasma is significantly decreased with age (from 1.65 h^{-1} at 35 years to 0.84 h^{-1} at 95 years). The peak concentration in the heart also increased with age (from 5536 to 7014 ng/ml), whereas the t_{max} was delayed with age (from 83 to 146 min; Table 4). The plasma pharmacokinetic parameters, C_{max}, A_1, λ_1, AUC, MRT and CL, for each age group (i.e. 35, 55, 75 and 95 years)

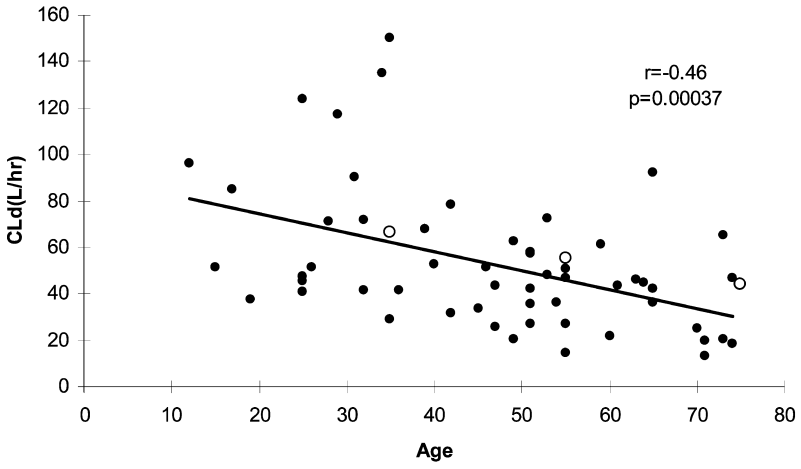

Fig. 3 Strong relationship between age and distribution clearance (CL_d) from the central compartment to the tissue compartments of 56 patients. The line is the least-squares linear regression line fit to the clinical data: $CL_d = -0.8171(age) + 90.684$, $r = -0.65$. The calculated CL_d from the PBPK model was located in the range of the CL_d from the 56 patients and showed a similar relationship with age as the clinical observations (● CL_d from the patients, ○ CL_d from the PBPK model)

are listed in Table 5. It is evident that the AUC for doxorubicin increased 15.89%, 38.58% and 94.32% relative to the AUC for a 35-year-old subject, consistent with decreasing CL with age. Doxorubicin AUC was highest in kidney followed by liver, heart and lean tissues. These findings are consistent with those reported by Cusack et al. [6] of a study in which daunorubicin pharmacokinetics in young and senescent rats were investigated. Again, the changes in early concentrations, AUC in different tissues and changes in distribution clearance with age are consistent with changes in blood flow through each tissue with age.

The doxorubicin plasma concentration-time course generated by the PBPK model for each age was subsequently fitted to a three-compartment model using WinNonlin. The pharmacokinetic parameters thus generated were incorporated into Eqs. 7 and 8 to regenerate values of V_c and CL_d corresponding to the specified ages. As expected, the value of V_c did not change with age (Table 6). However, the relationship between CL_d and age was consistent with that found by reanalysis of the clinical data reported by Robert et al. [7, 8, 9, 10, 11] (Fig. 3). Early phase kinetics of thiopental reported by Avram et al. [18] also demonstrate that V_c does not decrease with increasing age. In their study, the only pharmacokinetic variable that changed with age was CL_{21}, the intercompartmental clearance from the central compartment to the rapidly equilibrating peripheral compartment, the values of which decreased 35% between the ages of 20 and 80 years.

In patients with locally advanced breast cancer in whom doxorubicin pharmacokinetic parameters were also determined, a linear relationship was found between initial tumor regression and CL_d (Fig. 5).

Discussion

Studying the disposition and effects of cancer drugs in the elderly at the present time is an important endeavor. The population in America is aging. In 1900 just 4% of the population was 65 years or older. In the 1990s this had increased to 13% and by the year 2030, 21% of the population will be elderly [19]. Currently about 60% of all cases of cancer are in elderly people [19]. The impact of these changes is seen in the prediction that around 2030 the number of colon cancer patients will more than double [19].

The challenge of treating elderly cancer patients is not limited to the increase in patient population. It is important to realize that these patients do not always respond to chemotherapy in the same way as younger patients. For example, the absorption and disposition of anticancer drugs frequently changes with age [20]. In the elderly, a greater proportion of body weight is represented by fat. The volume of distribution of lipid-soluble drugs will therefore be higher per kilogram body weight. The larger volume of distribution will result in lower initial drug concentrations in the blood following single doses and longer half-lives. Conversely, both hepatic and renal clearance may be diminished with age producing higher serum drug concentrations during chronic drug administration [20]. In addition to altered pharmacokinetics, tissue sensitivity to the action of anticancer drugs may increase with age. The elderly are more sensitive to drug-induced mucositis, and cardiac and neurological toxicity, and to drugs producing myelosuppression [21]. Thus drug regimens suitable for younger patients may be significantly more toxic to elderly patients. Much less is known regarding the effect of age on the response of tumors to chemotherapy. For these reasons every opportunity to study the disposition and effects of age on antineoplastic dugs in elderly patients should be pursued.

In the study reported here we used previously reported results to evaluate the effects of age on the disposition of a widely used anticancer drug, doxorubicin [7, 8, 9, 10, 11]. In addition to the therapeutic benefits of the drug, doxorubicin can cause serious, and not infrequently, fatal congestive heart failure. An exacerbating factor for cardiotoxicity appears to be old age [3]. The reason for the increased sensitivity of heart tissue to doxorubicin in the elderly is not known with certainty. There may be an inherent increase in heart tissue sensitivity with age. As discussed by Cusack et al. [6], the enhanced sensitivity in

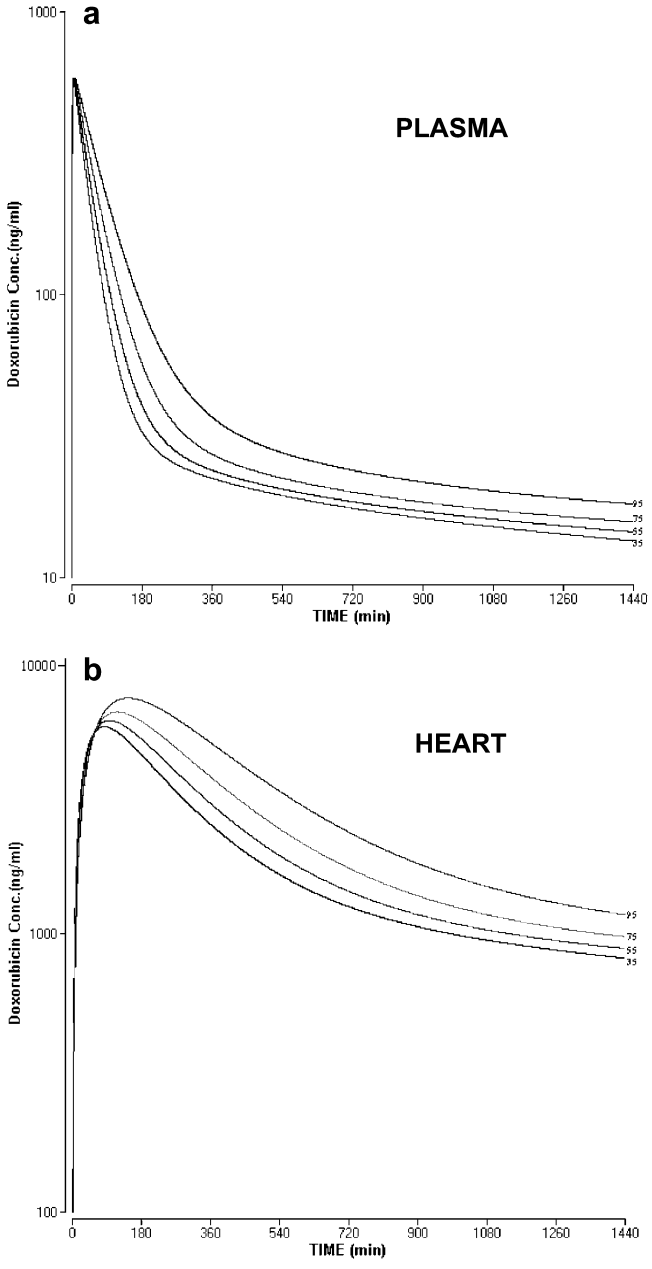

Fig. 4a, b Simulated (**a**) doxorubicin plasma concentration-time profile and (**b**) concentration-time profile in heart tissue for four age groups (35, 55, 75, 95 years) following administration of doxorubicin 50 mg by i.v. bolus

the elderly does not appear to be due to underlying heart disease. It is possible that the effects of anthracyclines on calcium metabolism by the sarcoplasmic reticulum in myocytes may increase the susceptibility of the aged myocardium to toxicity from anthracyclines. The cyclic reduction of anthracyclines producing free radicals coupled with the age-induced reduction in glutathione may leave the heart vulnerable to free radical attack. The specific contribution of these mechanisms to doxorubicin cardiotoxicity has not been fully resolved [6]. However, in the animal experiments described by Cusack et al., senescent rats demonstrated significantly higher early daunorubicin concentrations following i.v. bolus administration compared with younger animals [6]. Additional studies in rats have demonstrated that the rate of anthracycline administration affects the degree of cardiac damage. The same dose administered over a protracted time reduces the severity of cardiomyopathy [22]. Since the peak drug concentration can also be affected by the pharmacokinetics, changes in drug disposition may also influence the extent of cardiotoxicity. Hence, old age with its known effects on drug disposition could contribute to the enhanced sensitivity of the aged heart to anthracycline-induced cardiomyopathy.

Table 4 Simulated C_{max} and t_{max} of doxorubicin in heart tissue using the PBPK model for different age groups

Age group (years)	C_{max}(ng/ml)	t_{max}(min)
35	4616.78	83
55	4856.44	97
75	5207.96	117
95	5849.85	145

While much attention has been directed to the incidence and severity of adverse effects of cancer chemotherapy in the elderly, less interest has been paid to the effect of age on tumor response. With regard to doxorubicin, Preisler et al. [23] have demonstrated that the doxorubicin plasma concentration 3 h after administration was significantly correlated with the outcome of remission induction therapy in 45 patients treated for acute non-lymphocytic leukemia. Based upon our simulations with the PBPK model, doxorubicin concentrations in the study by Preisler et al. would still be in the distribution phase of drug disposition and thus may likewise be affected by CL_d.

The opportunity for exploring these mechanisms further in humans was made possible by the detailed studies of doxorubicin pharmacokinetics by Robert and coworkers. In several reports, these investigators determined the pharmacokinetics of doxorubicin in a large population. In each individual, following i.v. administration, the doxorubicin plasma concentration-time course was fitted to a three-compartment model. A principal observation in these studies was a linear dependence

Table 5 Pharmacokinetics of doxorubicin in plasma for different age groups from simulated data following administration of 60 mg doxorubicin by i.v. bolus

Age group (years)	C_{max} (ng/ml)	A_1 (ng/ml)	λ_1 (h^{-1})	AUC (ng min/ml)	MRT (h)	CL (l/h)
35	661.3	928.4	1.66	89,855	34.33	40.06
55	661.8	921.7	1.38	104,131	38.11	34.57
75	661.1	910.83	1.11	124,522	42.57	28.91
95	658.6	907.14	0.84	174,608	59.62	20.62

Table 6 Estimated central volume of distribution (V_c) and distribution clearance (CL_d) from simulated data for different age groups

Age group (years)	Central volume, V_c (l)	Distribution clearance, CL_d (l/h)
35	65.60	68.50
55	65.87	55.25
75	66.62	40.84
95	68.19	35.37

of a hybrid parameter, which the authors termed 'early clearance' and age. Since this term, as defined, is not very informative, we used pharmacokinetic methods developed subsequent to the publication of these studies to relate the age-dependent phenomena described by Robert et al. to parameters with more physiological associations [12]. Specifically, we determined the volume of the central compartment and the distribution clearance.

We found that the distribution clearance was highly correlated with age, whereas the volume of the central compartment was independent of age. A similar finding has been reported for thiopental disposition and age [18]. In the thiopental study, the reduction of the distribution clearance with age was attributed to a decline in regional blood flow with age.

Using a flow-dependent PBPK model for doxorubicin, we incorporated age-dependent changes in regional blood flows proposed for the thiopental PBPK model. The resulting simulations produced doxorubicin plasma concentrations that closely resembled the data of Robert et al. for patients of various ages. We therefore conclude that a possible contributor to the age-related doxorubicin cardiotoxicity is the altered doxorubicin concentration-time course in both plasma and heart tissue due to changes in regional blood flow with age. However, with the increased cardiotoxicity, there is also evidence of an increased therapeutic effect both in the treatment of non-lymphocytic leukemia and locally advanced breast cancer.

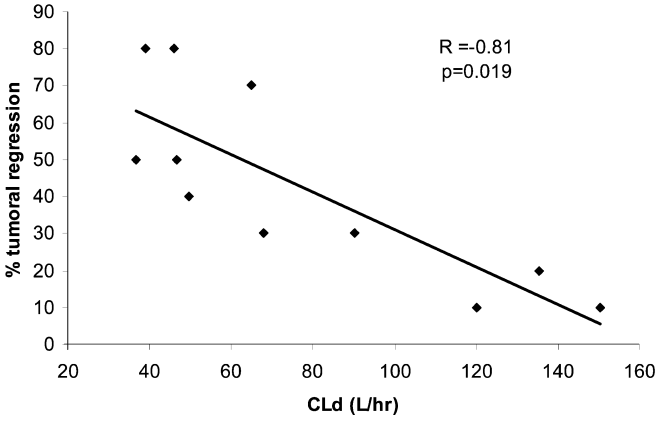

Fig. 5 Correlation between CL_d and tumor regression in 12 patients with locally advanced breast cancer ($r = -0.81$, $P = 0.019$)

Appendix

The differential equations for the PBPK model of doxorubicin

For lung:

$$V_{LU}\frac{dC_{LU}}{dt} = D + Q_{LI}\frac{C_{LI}}{R_{LI}} + Q_H\frac{C_H}{R_H} + Q_K\frac{C_K}{R_K} + Q_L\frac{C_L}{R_L} + Q_A\frac{C_A}{R_A} + Q_B\frac{C_B}{R_B} - (Q_{LI} + Q_H + Q_K + Q_L + Q_A + Q_B)\frac{C_{LU}}{R_{LU}}$$

For plasma:

$$V_P\frac{dC_P}{dt} = (Q_{LI} + Q_H + Q_K + Q_L + Q_A + Q_B)\left(\frac{C_{LU}}{R_{LU}} - C_P\right)$$

For liver:

$$V_{LI}\frac{dC_{LI}}{dt} = (Q_{LI} - Q_G - Q_S)\left(C_P - \frac{C_{LI}}{R_{LI}}\right) + Q_G\left(\frac{C_G}{R_G} - \frac{C_{LI}}{R_{LI}}\right) + Q_S\left(\frac{C_S}{R_S} - \frac{C_{LI}}{R_{LI}}\right) - CL\frac{C_{LI}}{R_{LI}}$$

For kidneys:

$$V_K\frac{dC_K}{dt} = Q_K\left(C_P - \frac{C_K}{R_K}\right)$$

For lean tissue:

$$V_L\frac{dC_L}{dt} = Q_L\left(C_P - \frac{C_L}{R_L}\right)$$

For adipose tissue:

$$V_A\frac{dC_A}{dt} = Q_A\left(C_P - \frac{C_A}{R_A}\right)$$

For bone marrow:

$$V_B\frac{dC_B}{dt} = Q_B\left(C_P - \frac{C_B}{R_B}\right)$$

For gastrointestinal tissue:

$$V_G\frac{dC_G}{dt} = Q_G\left(C_P - \frac{C_G}{R_G}\right)$$

For spleen:

$$V_S\frac{dC_S}{dt} = Q_S\left(C_P - \frac{C_S}{R_S}\right)$$

Nomenclature

D	Dose for i.v. bolus administration, nanograms
C	Concentration, nanograms per milliliter
CL	Total body clearance, milliliters per minute
Q	Plasma flow rate, milliliters per minute
R	Tissue-to-plasma equilibrium distribution ratio for linear binding
V	Volume, milliliters

Subscripts

G	Gastrointestinal tissue
K	Kidney
LI	Liver
L	Lean tissue
P	Plasma
B	Bone marrow
H	Heart
A	Adipose tissue
S	Spleen
LU	Lung

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