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ORIGINAL ARTICLE

Impact of body composition on pharmacokinetics of doxorubicin in children: a Glaser Pediatric Research Network study

Patrick A. Thompson · Gary L. Rosner · Katherine K. Matthay · Theodore B. Moore · Lisa R. Bomgaars · Kenneth J. Ellis · Jamie Renbarger · Stacey L. Berg

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Abstract
Purpose We studied the relationship between doxorubicin pharmacokinetics and body composition in children with cancer.
Patients and methods Children between 1 and 21 years of age, receiving doxorubicin as an infusion of any duration <24 h on either a 1-day or 2-day schedule were eligible if they had no significant abnormality of liver function tests, their dose of doxorubicin was not based on ideal body weight or otherwise "capped," and they weighed ≥12 kg. Body composition was measured by dual-energy X-ray absorptiometry. Doxorubicin and doxorubicinol concentration in plasma were measured by high pressure liquid chromatography. NONMEM was used to perform pharmacokinetic model fitting and S-PLUS was used to perform a post hoc analysis to examine the effect of body composition on pharmacokinetic parameters.
Results Twenty-two subjects (16 male; 10 Hispanic, 10 Caucasian, 2 Asian) completed the study. The median age was 15.0 years (range 3.3–21.5), median weight was 51.5 kg (range 12.4–80), median BMI was 19.7 (range 13.2–30.0), and median body fat was 25% (range 15–36). The population mean clearance of doxorubicin was 420 ml/min/m^2. Doxorubicinol but not doxorubicin clearance was lower in patients with body fat greater than 30%.
Conclusions Doxorubicinol clearance is decreased in children with >30% body fat. This finding is potentially important clinically, because doxorubicinol may contribute significantly to cardiac toxicity after doxorubicin administration. Further study of the body composition on doxorubicin and doxorubicinol pharmacokinetics and on clinical outcomes is warranted.

Keywords Doxorubicin · Doxorubicinol · Pharmacokinetics · Pediatrics · Body composition · Obesity

P. A. Thompson (✉) · L. R. Bomgaars · S. L. Berg
Texas Children's Cancer Center, 6621 Fannin St., MC3-3320, Houston, TX 77030, USA
e-mail: pathomps@txccc.org

G. L. Rosner
University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Box 1411, Houston, TX 77030, USA

K. K. Matthay
UCSF School of Medicine, 505 Parnassus Ave., Rm. M647, San Francisco, CA 94143, USA

T. B. Moore
UCLA David Geffen School of Medicine, 10833 Le Conte Ave., Rm. A2-312, Los Angeles, CA 90095, USA

K. J. Ellis
Children's Nutrition Research Center, 1100 Bates St., Rm. 4020, Houston, TX 77030, USA

J. Renbarger
Indiana University School of Medicine, 702 Barnhill Dr., Rm. 4340, Indianapolis, IN 46202, USA

Introduction

Doses of anticancer drugs are usually calculated based on body surface area (BSA) or body weight. This practice is based on the concept that hepatic and renal function, which account for most routes of drug clearance, are proportional to body size. In most studies, however, variability in overall drug clearance is only partially accounted for by variability in BSA. In addition, after equivalent BSA-based doses, some patients experience little toxicity while others may show severe toxic side effects [8]. Thus, the best way to

account for body size in anticancer drug dosing is unclear [2, 25, 27]. Furthermore, the appropriate modifications, if any, of anticancer drugs doses in very large obese patients remain unknown.

Many physiologic processes involved in the distribution, metabolism, and elimination of drugs may be altered in obese individuals. Obesity has been reported to affect the pharmacokinetics of several anticancer agents, as well as some antimicrobials and anesthetic agents [9, 19, 24, 35, 43]. The impact of obesity on pharmacokinetics, however, is not uniform. For example, the volume of distribution of a lipophilic drug might be significantly increased in obese patients. On the other hand, with some hydrophilic drugs the excess fat is not available for drug distribution, and the volume of distribution normalized to weight or surface area might significantly decrease [45]. For most drugs there are limited data evaluating the potential relationship between body composition and pharmacokinetics of specific agents. In cancer pharmacology, where drugs may have a narrow therapeutic window, a better understanding of this relationship is essential.

It seems intuitive that dosing an obese patient based on actual body size would carry an increased risk of toxicity. First, doses calculated based on true body size in obese patients can be 20–30% higher than the dose calculated for the same patient based on normal or ideal body weight [8]. In addition, the excess fat in an obese patient would not be expected to be particularly active as a site of drug clearance, while renal and hepatic drug clearance capacity would be expected to be impaired rather than increased in severe obesity [4, 11, 14, 22, 34, 37]. Thus, doses based on true body size might appear to represent "too much" chemotherapy, and anticancer drug doses are often reduced a priori in very large patients.

Recent data, however, suggest that empiric dose reductions are undesirable in cancer therapy. A number of studies have demonstrated that the toxicity of therapy is the same or less in obese patients compared with normal weight patients [23, 26, 41, 44]. In some groups of patients, disease outcome is worse in obese patients treated with reduced doses [12, 44].

The problem of appropriate drug dosing is particularly acute in pediatric oncology, where the spectrum from underweight to obesity is superimposed on normal age-related differences in children's size. The pediatric data related to influence of obesity on outcomes or pharmacokinetics of anticancer drugs are sparse. Treatment related mortality was higher in overweight children with acute myeloid leukemia in a recent Children's Cancer Group study, although neutrophil count data did not suggest that these patients were receiving excessive chemotherapy doses [32]. In contrast, a large retrospective study showed no influence of body mass index (BMI) on outcome in children with acute lymphoblastic leukemia [29]. Furthermore, a recent study showed that children with acute myeloid leukemia who had a complete response to induction therapy had higher plasma doxorubicin concentrations than those who did not enter remission [40], supporting the hypothesis that lower drug doses could compromise treatment efficacy.

In order to explore whether changes in doxorubicin dosing should be considered in very large or obese children, we prospectively studied the relationship between doxorubicin pharmacokinetics and body composition in children with cancer.

Methods

Subjects

Institutional Review Board approval and informed consent and assent were obtained according to federal and institutional guidelines. Eligible subjects were between 1 and 21 years of age, receiving chemotherapy that included doxorubicin administered as an infusion of any duration <24 h, on either a 1-day or 2-day schedule. Women who were known to be pregnant or lactating, patients with significant uncontrolled systemic illness, and those whose serum glutamic oxaloacetic transaminase (SGOT/AST) or serum glutamic pyruvate transaminase (SGPT/ALT) was greater than three times the upper limit of normal, whose bilirubin was greater than upper limit of normal, whose dose of doxorubicin was based on ideal body weight or otherwise "capped," or who weighed <12 kg (due to blood sampling volume constraints) were excluded.

Evaluations

Subjects were weighed wearing light clothing and no shoes. Height was measured using a stadiometer. BMI was calculated as BMI = 10,000 $\times$weight (kg)/height (cm)^2. *Z*-scores for BMI (zBMI) were obtained from the Centers for Disease Control and Prevention website (http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/datafiles.htm). Complete blood count (CBC) with differential and platelet count, SGOT/AST, SGPT/ALT, bilirubin, blood urea nitrogen (BUN), creatinine, total protein, albumin, prothrombin time/partial thromboplastin time (PT/PTT), alkaline phosphatase, and gamma glutamyl transferase (GGT) were obtained no more than 14 days prior to doxorubicin administration and were repeated at the time of doxorubicin administration if the subjects had an intervening illness. All specimens were analyzed by a central laboratory. Body composition testing was performed within 7 days before or after administration of the dose of doxorubicin using dual-energy X-ray absorptiometry (DXA) with a Hologic 4500A/4500W Delphi operated in the whole-body mode.

Pharmacokinetic sampling

Blood samples were drawn from a site different from the infusion site. For single dose regimens, samples were obtained in sodium heparin tubes prior to the drug infusion, at the midpoint of the infusion for infusions ≥30 min duration, and at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 (when feasible), 24 and 48 h after the end of the infusion. For regimens with doxorubicin dosing on two days, the samples were obtained on day 1 prior to the drug infusion, and at 0, 0.5, 1, 2, 4, and 6 h after the end of the day 1 infusion and immediately prior to the day 2 infusion, then at 0, 0.5, 1, 1.5, 2, 4, 6, 8, and 12 (when feasible), 24 and 48 h after the end of the day 2 infusion. Each sample was placed immediately on wet ice and centrifuged at 4°C at 2,500 rpms for 10 min within 15 min of collection. Plasma was separated and stored at −70°C or −20°C until analysis.

Pharmacokinetic method

Doxorubicin was purchased from Ben Venue (Bedford, OH). Doxorubicinol was purchased from Custom Synthesis Services (Madison, WI). Doxorubicin and doxorubicinol concentrations were measured using a variation of previously published high performance liquid chromatography assay [3, 16]. In brief, plasma samples were spiked with daunomycin as internal standard, then underwent solid phase extraction using Nexus cartridges conditioned with 1 ml methanol followed by 1 ml water. After loading 0.5 mL of plasma mixed with 0.5 mL 1% phosphoric acid the sample was rinsed with water and 5% acetonitrile then eluted with acetonitrile. Eluates were evaporated to dryness under nitrogen at 37°C. Prior to injection onto the HPLC system samples were reconstituted in 0.5 m of 1% phosphoric acid.

A total of 100 μL of reconstituted sample were injected via a Model 717 Plus Autosampler (Waters, Inc) onto a Luna C18(2), 3 μm, 4.6 mm × 150 mm analytic column with a Phenomenex C18, 2 mm × 3 mm, 3μ guard column and eluted with a gradient consisting of solvent A (75% 20 mM KH_2PO_4 with 1 mL/L H_3PO_4/25% acetonitrile v/v) from 0 to 7 min followed by solvent B (60% 20 mM KH_2PO_4 with 1 mL/L H_3PO_4/40% acetonitrile) from 7 to 11 min followed by solvent A from 11 to 20 min at an isocratic flow rate of 1 ml/min. Peaks were monitored on a Model 474 Scanning Fluorescence Detector (Waters, Inc) with an excitation wavelength of 480 nm and an emission cutoff of 550 nm. The retention times were 4 min for doxorubicinol, 8 min for doxorubicin, and 15 min for daunomycin. Recovery of doxorubicin and doxorubicinol was approximately 80%. The limit of quantitation of doxorubicin and doxorubicinol was 2 ng/ml, and the standard curve was linear from 0.01 to 20 μg/ml. The intraday and interday coefficients of variation were less than 7%.

Pharmacokinetic model

We modeled the pharmacokinetics of doxorubicin and doxorubicinol using NONMEM VI (GloboMax, Hannover, MD). Model fitting was performed on a personal computer using a DIGITAL Visual FORTRAN compiler (Version 6.1). Exponential error models were used to describe the interindividual variance in each pharmacokinetic parameter, and the residual error model included proportional and additive terms.

Different models with varying numbers of compartments for doxorubicin and doxorubicinol were tested. Based on inspection of the concentration time curves for doxorubicin, two- and three-compartment models were considered. For doxorubicinol, one- and two-compartment models were evaluated. Model selection was based on the fit of the model to the data as approached by graphical plots.

In the final model, all pharmacokinetic parameters were linearly scaled based on BSA. We chose BSA scaling because it is commonly applied in oncology for size-based dose adjustments and is well accepted by clinicians. We also evaluated allometric scaling, but the individual patient estimates of PK parameters were not significantly different and therefore did not impact our post hoc analysis of the effect of body composition.

Analysis of the effect of body composition

To examine the significance of body composition on pharmacokinetics we performed two analyses. First, we compared the pharmacokinetic parameters of those patients who had increased body fat (body fat >30%) to those who did not (body fat <30%). To make these comparisons we used the Wilcoxon Rank Sum test. All quoted *P* values are two-sided, and we considered a *P* value less than 0.05 to be statistically significant. Statistical calculations were made with S-PLUS for Windows Version 6.2. We then compared the individual pharmacokinetic parameters determined for those patients classified as overweight (BMI >85th percentile for age) to those who were normal weight or underweight. No *P* values were calculated for this comparison since there were only two patients in the overweight group based on BMI. We also examined plots of the estimated pharmacokinetic parameters against the baseline clinical laboratory results, doxorubicin dose, and infusion duration to determine if any of these variables contributed to interpatient variability in pharmacokinetic parameters.

Results

Twenty-two subjects (16 male; 10 Hispanic, 10 Caucasian, 2 Asian) completed the study. Subject characteristics are shown in Table 1. The median age was 15.0 years (range 3.3–21.5), median weight was 51.5 kg (range 12.4–80), median BMI was 19.7 (range 13.2–30.0), and median body fat was 25% (range 15–36). Six patients had body fat >30%. Five patients were underweight (BMI <10th percentile for age), 15 were normal weight (BMI 10th–85th percentile), and two were overweight (BMI >85th percentile). Three of the patients with greater than 30% body fat were male and three were female. The age range of the patients in this group was 9–21, with an average age of 16. Four of the patients were white and two were Asian. There were no obvious correlations among body fat, race, and ethnicity in this study. Higher body fat content did appear to be associated with age. Of the six patients less than 10 years of age in this study only one had a body fat content greater than 30%.

The best model for doxorubicin and its metabolite doxorubicinol consisted of a total of four-compartments, three compartments for doxorubicin and one for doxorubicinol (Fig. 1). All parameters were linearly scaled based on BSA. The point estimates, standard errors, and coefficients of variation (for interindividual variance terms) are presented in Table 2 for this base model.

Predicted versus observed doxorubicin and doxorubicinol concentration plots are shown in Fig. 2a, b. Concentrations corresponding to patients with <30% body fat are represented with open diamonds. Concentrations corresponding to patients with >30% body fat are represented with closed circles. Larger open circles are used to distinguish concentrations corresponding to patients whose BMI was greater than the 85th percentile for age. The solid 45 degree-line represents exact agreement between predicted and measured concentrations. As these curves show, the

Table 1 Patient characteristics

Age (year; median)	15
(range)	(3.3–21.5)
Gender	16 male, 6 female
Ethnicity	10 Hispanic
	10 Caucasian
	2 Asian
Weight (kg)	51.5
	(12.4–80)
BMI (kg/m^2)	19.7
	(13.2–30.0)
Bodyfat (%)	24.7
	(15.4–36.4)
Diagnoses (#)	Hodgkin Disease (6)
	Acute lymphoblastic leukemia (4)
	Burkitt's lymphoma (3)
	Non-Hodgkin lymphoma (3)
	Osteosarcoma (3)
	Neuroblastoma
	Synovial sarcoma
	Hepatoblastoma

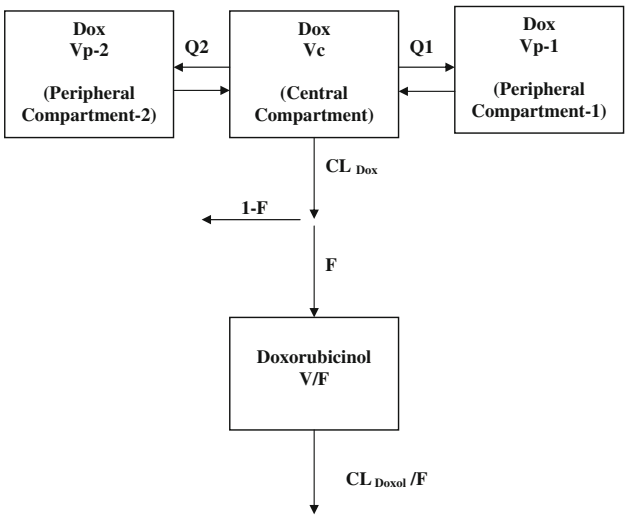

Fig. 1 Schematic of population pharmacokinetic model for doxorubicin and doxorubicinol. The model includes three compartments for doxorubicin and one for doxorubicinol. Parameters are defined as follows: (1) V_c is the volume of distribution of central doxorubicin compartment, (2) V_{p-1} is the volume of distribution of the first doxorubicin peripheral compartment, (3) V_{p-2} is the volume of distribution of the second doxorubicin peripheral compartment, (4) CL is clearance of doxorubicin, (5) Q_1 is the intercompartmental clearance of doxorubicin between the central compartment and the first peripheral compartment, (6) Q_2 is the intercompartmental clearance of doxorubicin between the central compartment and the second peripheral compartment (7) F is the fraction of doxorubicin metabolized to doxorubicinol, (8) V/F is the apparent volume of distribution of doxorubicinol, and (9) CL/F is the apparent clearance of doxorubicinol

Table 2 Estimates for mean population pharmacokinetic parameters from NONMEM

Parameter	Point estimate	Units	SE	%RSE
Doxorubicin pharmacokinetic parameters				
CL	25.1	L/m^2/h	1.76	7.0
V_c	6.96	L/m^2	1.12	16.1
Q_1	24.8	L/m^2/h	4.11	16.6
V_{P1}	557	L/m^2	72.6	13.0
Q_2	6.59	L/m^2/h	2.05	31.1
V_{P2}	16.5	L/m^2	6.87	41.6
Doxorubicinol pharmacokinetic parameters				
CL/F	50.2	L/m^2/h	5.40	10.8
V/F	1,100	L/m^2	141	12.8

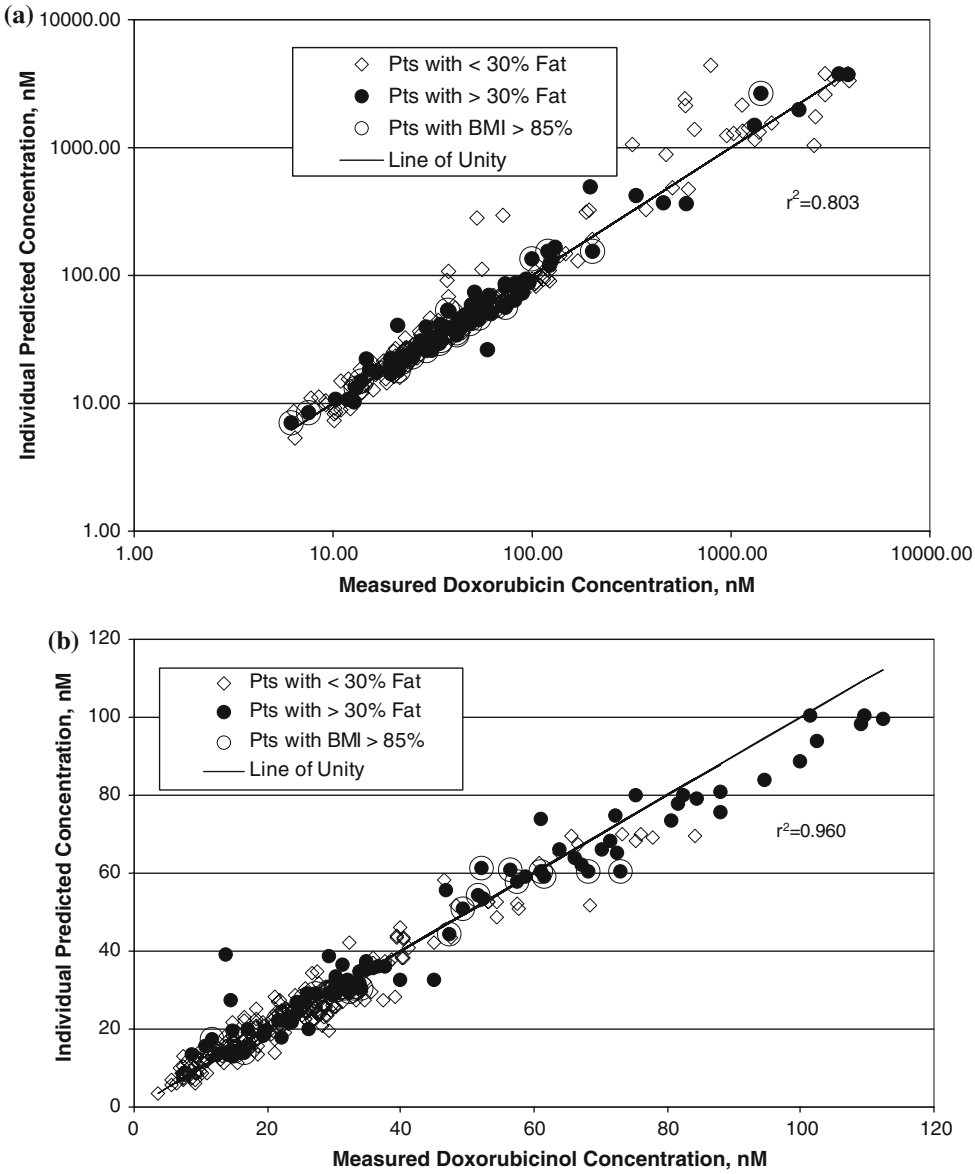

Fig. 2 **a** Scatterplot of doxorubicin predicted concentrations versus observed concentrations. The line of identity is included for comparison. Concentrations corresponding to patients with <30% body fat are represented with open diamonds. Concentrations corresponding to patients with >30% body fat are represented with closed circles. Concentrations corresponding to patients having a BMI >85% are indicated by larger open circles. The *R*-squared value is 0.803. **b** Scatterplot of doxorubicinol predicted concentrations versus observed concentrations. The line of identity is included for comparison. Concentrations corresponding to patients with <30% body fat are represented with *open diamonds*. Concentrations corresponding to patients with >30% body fat are represented with *closed circles*. Concentrations corresponding to patients having a BMI >85% are indicated by *larger open circles*. The *R*-squared value is 0.960

model generally fit the concentration data well for the whole patient population, including those who had high body fat content (body fat >30%) or were overweight (BMI >85th percentile). However, as shown in Fig. 2a, there is some variability between measured and predicted concentrations at the highest concentrations of doxorubicin. This is not surprising because the highest concentrations are from samples taken immediately after short (5–15 min) infusions. Any uncertainty or deviation in the infusion duration or sampling time would introduce uncertainty into these estimates. In contrast, the concentration time profile for the metabolite doxorubicinol is less sensitive to infusion time and the model fit over the entire observed concentration range is excellent.

Measured body size and body composition variables are shown in Table 3 for each patient along with the estimated individual pharmacokinetic parameters. Shaded rows indicate patients with >30% body fat and bold-face type indicates patients with a BMI >85th percentile. As shown in the table, the between patient variability appears less for the

Table 3 Individual patient pharmacokinetic parameters (*shaded rows* indicate patients with >30% body fat and *bold-face type* indicates patients with BMI >85th percentile)

Patient ID	BMI (kg/m^2)	AGE (yr)	WT (kg)	BSA (m^2)	BMI (%)	FAT (%)	Doxorubicin						Doxorubicinol	
							CL ($L/hr/m^2$)	Vc (L/m^2)	Q_1 ($L/hr/m^2$)	$V_{P\text{-}1}$ (L/m^2)	Q_2 ($L/hr/m^2$)	$V_{P\text{-}2}$ (L/m^2)	CL/F ($L/hr/m^2$)	V/F (L/m^2)
1501	16.89	16.3	51.9	1.59	2.9	17.4	32.0	11.73	35.11	664	12.7	30.4	59.1	1740
1502	20.08	18.7	54.0	1.60	31.2	21.9	23.3	4.97	27.29	613	5.1	12.9	50.8	819
1503	**29.96**	**15.8**	**80.0**	**1.91**	**97.6**	**34.7**	**25.5**	**7.30**	**20.55**	**489**	**5.1**	**13.0**	**25.4**	**443**
1507	13.82	6.5	17.4	0.74	6.4	22.1	33.9	5.02	28.22	616	9.4	23.0	170.1	2803
1509	16.32	10.6	30.8	1.08	37.1	26.4	29.5	5.89	32.81	656	6.2	15.5	55.6	1119
1510	20.74	14.7	51.0	1.49	65.0	27.8	17.0	4.83	7.16	283	1.1	3.0	69.3	1912
4501	16.61	5.7	22.0	0.85	80.5	20.8	24.7	5.42	18.59	483	2.9	7.6	104.5	2747
4502	21.38	16.1	68.2	1.84	60.3	15.8	33.0	11.47	38.97	727	10.5	25.5	48.7	1427
4503	21.68	13.9	55.5	1.54	79.8	29.9	32.3	8.80	29.46	632	10.7	25.9	74.1	1312
4504	14.74	12.0	33.6	1.19	3.3	18.6	22.1	9.55	15.99	436	6.3	15.7	56.9	1445
4505	13.20	5.7	15.4	0.68	0.8	22.9	16.7	3.78	22.82	512	8.2	20.3	27.9	574
5501	16.51	6.9	22.6	0.86	73.9	21.9	27.2	6.93	23.09	522	9.2	22.6	93.5	1944
5502	22.95	21.5	59.5	1.63	63.3	34.7	25.7	6.44	15.88	443	2.7	7.3	61.6	1676
5503	21.72	17.6	57.5	1.61	57.2	33.4	22.5	8.16	16.89	446	9.9	24.1	36.8	629
5504	20.35	19.7	55.0	1.57	16.5	16.4	26.4	7.71	29.09	633	8.1	20.0	49.3	1126
5505	23.91	17.1	77.9	2.06	78.2	36.2	21.2	7.73	35.41	621	4.1	10.6	25.5	352
5506	14.59	3.3	12.4	0.56	10.8	19.4	28.6	10.91	50.89	833	9.3	22.7	41.3	1443
5507	18.31	14.1	41.2	1.34	35.0	29.3	31.7	8.18	36.69	707	10.1	24.5	61.4	1190
5508	19.26	15.2	49.0	1.47	39.4	28.0	22.6	4.90	21.65	520	5.2	13.1	54.2	987
5509	**21.29**	**9.3**	**40.3**	**1.24**	**94.9**	**33.7**	**24.7**	**9.23**	**28.44**	**587**	**13.2**	**31.5**	**26.5**	**599**
5510	22.02	20.9	52.9	1.51	53.5	32.0	28.2	7.20	24.25	575	6.7	16.8	47.6	1114
5511	18.78	21.4	53.0	1.57	3.3	15.4	15.7	5.04	18.28	462	7.6	18.9	20.3	630
Mean	19.3	13.8	45.5	1.36	45.0	25.4	25.6	7.3	26.3	566	7.5	18.4	57.3	1274
Median	19.7	15.0	51.5	1.50	46.5	24.7	25.6	7.3	25.8	581	7.9	19.5	52.5	1158
Std Dev	3.91	5.54	19.3	0.41	32.3	6.9	5.3	2.3	9.7	121	3.2	7.6	33.0	673

doxorubicin pharmacokinetic parameters compared to the doxorubicinol parameters. For example the doxorubicin clearance is 25.6 ± 5.3 L/m^2/hr (mean $\pm$ standard deviation), which represents a coefficient of variation of 21%. On the other hand, the apparent doxorubicinol clearance is 57.3 ± 33 L/m^2/h, which represents a coefficient of variation of 58%.

To evaluate the impact of body composition on pharmacokinetics, we compared the estimated pharmacokinetic parameters in patients with body fat content greater than 30% to those less than 30%. We also used BMI percentile to classify patients as underweight (<10 percentile), normal weight (10–85th percentile), or overweight (>85th percentile) and compared the estimated pharmacokinetic parameters for patients in each group.

In patients with body fat greater than 30%, we observed that the apparent doxorubicinol volume of distribution and clearance were lower than in patients with body fat less than 30% ($P < 0.05$). These results are summarized in Table 4. We also observed that the doxorubicinol volume of distribution and clearance was lower in the two patients who were overweight by BMI criteria (BMI >85th percentile) compared to normal weight (BMI 10th–85th percentile) or underweight patients (BMI <10th percentile). No statistical significance is claimed for this comparison. These results are summarized in Table 5.

Table 4 Effect of percentage body fat on doxorubicin and doxorubicinol pharmacokinetic parameters

Parameter (units)	FAT % <30 (Mean $\pm$ SD) $N = 16$	FAT % >30 (Mean $\pm$ SD) $N = 6$	P value
CL—Doxorubicin ($L/h/m^2$)	26.0 ± 6.0	24.6 ± 2.5	0.41
V_c—Doxorubicin (L/m^2)	7.2 ± 2.6	7.7 ± 0.9	0.49
Q_1—Doxorubicin ($L/h/m^2$)	27.3 ± 10.4	23.6 ± 7.4	0.41
V_{p-1}—Doxorubicin (L/m^2)	581 ± 133	527 ± 77	0.23
Q_2—Doxorubicin ($L/h/m^2$)	7.7 ± 3.1	7.0 ± 3.9	0.59
V_{P-2}—Doxorubicin (L/m^2)	18.9 ± 7.2	17.2 ± 9.1	0.59
CL/F—Doxorubicinol (L/h/m2)	64.8 ± 35.1	37.2 ± 14.9	0.033
V/F—Doxorubicinol (L/m^2)	$1{,}450 \pm 654$	802 ± 503	0.021

Table 5 Effect of BMI on doxorubicin and doxorubicinol pharmacokinetic parameters

Parameter (units)	BMI <10% (Mean ± SD) $N = 5$	BMI 10–85% (Mean ± SD) $N = 15$	BMI >85% $N = 2$	
			Pt # 1503	Pt # 1509
CL—Doxorubicin (L/h/m^2)	24.1 ± 8.5	26.2 ± 4.5	25.5	24.6
V_c—Doxorubicin (L/m^2)	7.0 ± 3.4	7.3 ± 2.0	7.3	9.2
Q_1—Doxorubicin (L/h/m^2)	24.1 ± 7.7	27.2 ± 10.9	20.6	28.4
V_{p-1}—Doxorubicin (L/m^2)	538 ± 99	579 ± 136	489	587
Q_2—Doxorubicin (L/h/m^2)	8.8 ± 2.4	6.8 ± 3.2	5.1	13.2
V_{P-2}—Doxorubicin (L/m^2)	21.7 ± 5.6	16.8 ± 7.5	13.0	31.5
CL/F—Doxorubicinol (L/h/m^2)	66.8 ± 60.2	58.3 ± 20.6	25.4	26.5
V/F—Doxorubicinol (L/m^2)	1,440 ± 916	1,320 ± 588	443	599

To screen for the effect of other factors on pharmacokinetics, we used S-PLUS to examine plots of each pharmacokinetic parameter against the available clinical variables (age, sex, and baseline laboratory values). There were no statistically significant relationships observed. This was an expected result since the study excluded patients with significant abnormalities in organ function and baseline laboratory values. Similarly we did not observe any impact of drug administration (infusion duration or dose) on the pharmacokinetic parameters. Patients were on numerous concomitant medications and it was not possible to analyze this effect.

We also performed sequential covariate modeling (results not shown) to determine whether body fat was a significant covariate in the population model. Inclusion of body fat as a covariate for doxorubicinol clearance and volume of distribution improved the model. However, we have chosen to emphasize the post hoc analysis because sequential covariate modeling with small data sets is controversial [42]. In addition, the post hoc analysis should be sufficient for an exploratory, hypothesis generating study such as this.

Discussion

This is the first study to evaluate the effect of body composition on doxorubicin and doxorubicinol pharmacokinetics in children. Previous data on doxorubicin pharmacokinetics in children are relatively sparse and often based on a limited number of samples per patient. As with adult data, the pediatric data show variability on the order of a magnitude in doxorubicin clearance even within single studies [13, 18, 21, 28, 40]. The population mean clearance of 25.6 L/h/m^2 (approximately 430 ml/min/m^2) in our study is in good agreement with that published for both children [21, 40] and adults (reviewed in [17]). Both two and three-compartment models have been published for doxorubicin pharmacokinetics [7, 30]. In breast cancer patients Camaggi et al. [7] determined that three half-lives of doxorubicin were 4.8 min; 2.57 h, and 48.4 h. In our study, the means of the three half-lives were 5.2 min, 1.98 h, and 31.9 h, when we back-calculated them from our estimates of the PK parameters.

Data on doxorubicinol are more limited, but the results we report are similar to what has been reported by other investigators [6, 31]. Joerger et al. [31] developed a population pharmacokinetic model in breast cancer patients from which they estimated a population mean apparent clearance of doxorubicinol (CL/F) of 108 L/h. Assuming a BSA of 1.7 m^2 for an adult patient, this corresponds to 63.5 L/m^2/h which is close to our estimated population mean of 50.2 L/m^2/h. Similarly, their population mean apparent volume of distribution (1,580 L or approximately 929 L/m^2) is in good agreement with our estimate (1,100 L/m^2).

In evaluating the effect of body composition on pharmacokinetics in children there are two significant challenges: (1) selecting the appropriate methodology for adjusting (normalizing or scaling) pharmacokinetic parameters for size, and (2) choosing the appropriate definition of abnormal body composition or obesity. In this study (as in all pediatric pharmacokinetic studies) we had to normalize or scale the pharmacokinetic parameters to adjust for the normal age-related differences in patient size. We chose empiric BSA scaling for our model because the individual patient estimates of pharmacokinetic parameters with this approach were not significantly different from those we obtained using allometric scaling and this approach is the standard for size adjustment in oncology dosing.

The appropriate definition of obesity in childhood is debated, but in general it is based on BMI adjusted for age [10]. There is also a suggestion that body fat >25% for boys and >30–35% for girls can define obesity [1, 33]. In our study, we had only two patients who based on BMI were overweight, so we also evaluated the effect of body composition using fat content.

When we divided subjects into groups by body fat of more or less than 30%, doxorubicin pharmacokinetic parameters were not significantly different between the groups. In addition, doxorubicin parameters were not different in the two patients with a BMI percentile >85%. This is

consistent with previous studies showing no relationship between BMI and end-of-infusion plasma doxorubicin concentrations in children with ALL or lymphoma [21, 28], though another study reported a trend towards higher peak concentrations of doxorubicin in children with a low BMI [18]. In contrast, we found that apparent doxorubicinol clearance is lower and apparent doxorubicinol volumes of distribution smaller in patients with body fat >30% ($P < 0.05$). Similarly, the two patients in the overweight BMI percentile category showed lower doxorubicinol clearance and smaller doxorubicinol volumes of distribution. Although not statistically different, these two data points do suggest that future studies of doxorubicin pharmacokinetics should continue to look at the question of how obesity may impact doxorubicinol disposition.

In summary, our data suggest that doxorubicinol clearance may be decreased in children with >30% body fat. This finding is potentially important clinically, because doxorubicinol may contribute significantly to cardiac toxicity after doxorubicin administration [5, 15, 20, 36, 38, 39, 46, 47]. Of note, although the two patients in our study in the overweight BMI percentile category had body fat >30%, the other four patients with body fat >30% were in the normal weight range by BMI percentile for age (Table 3). Thus, use of BMI percentile alone may not be adequate to identify children at risk for altered doxorubicinol pharmacokinetics. Further study of the effect of obesity and body composition on doxorubicin and doxorubicinol pharmacokinetics and on clinical outcomes is warranted. Moreover, because childhood obesity is a growing epidemic, the analysis of body size and composition effects should be considered in all pharmacokinetic studies of anticancer agents in children. At a minimum, pediatric PK studies should examine the relationship between BMI and pharmacokinetics; and, if possible, body fat content should be measured as well. In order to facilitate accrual to such studies, limited sampling schemes, reduced sample volumes, population modeling techniques, and other methods to reduce the need for frequent pharmacokinetic sampling should also be considered. Identifying and understanding what effects body composition may have on drug disposition represents an important step toward "personalizing" and improving therapy.

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