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Pharmacokinetics of Doxorubicin in Children With Acute Lymphoblastic Leukemia: Multi-Institutional Collaborative Study

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Background. In adults, it has been shown that the pharmacokinetics of doxorubicin are highly variable, despite standardization of the dose based on body surface area (BSA). The purpose of this study was to determine the plasma concentrations of doxorubicin and its active metabolite doxorubicinol in children treated for acute lymphoblastic leukemia (ALL). ***Procedure.*** Children, 107 in number, aged 1.3–17.3 years, were studied at Day 1 of induction therapy according to the current Nordic protocol. Five infants, 3–9 months old, were also included. Plasma samples were drawn 23 hr after the start of a 24-hr infusion of doxorubicin 40 mg/m^2, and analyzed by reversed-phase liquid chromatography. ***Results.*** There was a more than 10-fold difference between patients in dose normalized plasma concentration of doxorubicin, median 62.8 ng/ml, range 22.6–334 ng/ml. The doxorubicin concentrations differed significantly between age groups ($P=0.003$). Children aged 4–6 years had the highest doxorubicin concentrations, median 77.9 ng/ml, followed by 2–4-year-old children, median 64.3 ng/ml. Both younger and older children had median values of about 50 ng/ml. Patients with white blood cell (WBC) count $> 50 \times 10^9$/L at diagnosis had significantly lower doxorubicin concentrations, median 55.3 ng/ml, than those with WBC count $< 10 \times 10^9$/L, median 64.4 ng/ml ($P=0.015$). There was no difference in doxorubicin concentration between boys and girls. No correlation was found between doxorubicin levels and serum aminotransferases or serum creatinine. The concentration of doxorubicinol was 13% (median value) of that of doxorubicin. Four infants, 7–9 months old, had plasma clearance between 350–431 ml/min/m^2, which is in the same range as in older children. A 3-month-old infant had a clearance of 181 ml/min/m^2. ***Conclusions.*** The age groups who had the highest doxorubicin concentrations, (2-) 4–6-year-old children, are known to make up a large proportion of standard risk ALL cases with good prognosis. The correlation between doxorubicin plasma levels and clinical effect needs further study. The influence of age, body composition, and tumor burden on the pharmacokinetics of antineoplastic drugs should also be further explored, aiming at improvements in the current dosing regimen based on BSA. Med Pediatr Oncol 2002;38:329–337.

Key words: doxorubicin; anthracycline; pharmacokinetics; childhood cancer; acute lymphoblastic leukemia

INTRODUCTION

The anthracycline doxorubicin is widely used in the treatment of malignant disease, including leukemias and many different solid tumors [1,2]. In adults it has been shown that the pharmacokinetics of the drug are highly variable, with an almost ten-fold inter-patient variation of the area under the plasma concentration–time curve (AUC), despite standardization of the dose based on body surface area (BSA) [2–5]. The reason for the high variability of doxorubicin pharmacokinetics is largely unknown, but it has been suggested that there might be a need for dose reduction in patients with elevated serum aminotransferases and/or serum bilirubin [3]. Only scant information is available concerning pharmacokinetic interaction of the anthracyclines with other anti-neoplastic drugs [2]. A change in doxorubicin pharmacokinetics in combination with taxanes has been attributed to the drug solvent and not the taxanes [6,7].

Side effects of doxorubicin include nausea and vomiting, mucositis, myelosuppression, and cardiotoxicity. The risk for cardiomyopathy is related to the

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cumulative dose [8], but there also appear to be differences in sensitivity between individuals [9]. The considerable inter-individual differences in doxorubicin pharmacokinetics, together with unpredictable variability in toxicity and outcome of therapy, has led to a discussion of whether doxorubicin might be a candidate for therapeutic drug monitoring [10,11].

Previous publications on the pharmacokinetics of doxorubicin in children are few, and some only in abstract form 15 years ago or more [12–14]. In a recent work, data on doxorubicin and 4′-epi-doxorubicin were presented for 31 children with acute lymphoblastic leukemia (ALL) [15]. All these reports are from single-center studies with relatively small patient numbers, and/or patients treated for a variety of malignancies. Clear age dependency or gender differences have not been observed. Dose normalized steady state concentrations of doxorubicin tended to be higher in patients with low body mass index (BMI), but the difference was not statistically significant [15].

The aim of the present investigation was to study the pharmacokinetics of doxorubicin and its active metabolite doxorubicinol in children with ALL, treated according to the current Nordic protocol at six Swedish centers for pediatric oncology. We were interested in estimation of the magnitude of variation in the plasma concentrations achieved in a routine clinical setting, and how this correlated to treatment center, age, gender, liver and renal function parameters, BMI, and tumor burden at diagnosis. The maximum plasma concentration, reached at the end of a constant infusion, can be used as a substitute for measuring AUC. This simplified technique of pharmacokinetic monitoring, which is well documented for the anthracyclines [15,16], was used in the present study.

PATIENTS AND METHODS

Patients

Between February 1995 and November 1999, 112 children with ALL were included in the study. All Swedish centers for pediatric oncology participated: Uppsala (n = 35), Stockholm (n = 31), Umeå (n = 19), Göteborg (n = 11), Lund (n = 10), and Linköping (n = 6). During this time period, about 300 children in Sweden were diagnosed with ALL, i.e., our patient material represents 1/3 of the whole patient population. Reasons for not including children were practical difficulties, such as lack of extra venous access or lack of staff to handle research samples, or refusal of patients or parents to participate.

Children (> 1 year). Children, 107 in number, > 1 year of age, with newly diagnosed ALL, treated according to the Nordic (NOPHO ALL-92) protocol [17], were studied on treatment Day 1. There were 44 girls and 63 boys, with a median age of 4.8 years (range 1.3–17.3). Children, 35 in number (33%), were classified as standard risk (SR) ALL, 42 (39%) as intermediate risk (IR), and 30 (28%) as high risk (HR) ALL. These figures, as well as the age distribution of the patients, are very similar to data reported for the whole cohort of children treated according to this protocol.

Doxorubicin was dissolved in 500–2000 ml fluid containing 50 g glucose per liter and administered by constant infusion pump over a 24-hr period, either in a central (most cases) or peripheral venous catheter. The NOPHO ALL-92 protocol includes administration of doxorubicin 40 mg/m^2 BSA on treatment Day 1 to patients in all risk groups. This infusion is preceded by injection of vincristine 2 mg/m^2 (max. dose 2 mg), given as an i.v. bolus injection. Treatment with oral prednisolone 60 mg/m^2 and allopurinol 300 mg/m^2 is given concomitantly. Fluid (i.v.) containing 50 g glucose, 42 mmol $NaHCO_3$, and 20 mmol KCl per liter is also administered to a total volume of 3 L/m^2/24 hr. In the HR group, most patients received increasing doses of prednisolone 2–5 days, before the administration of doxorubicin and vincristine.

Infants. Five infants, 3–9 months old, with newly diagnosed ALL were treated according to various protocols. They were all studied on Day 1 after receiving doxorubicin 12.2–37.6 mg/m^2 as a 24 hr i.v. infusion (Table I).

Patients and/or parents gave informed consent. The local Ethics committees approved the study.

Plasma Samples

Blood was usually drawn from a peripheral vein (never from the catheter used for drug infusion) and collected in a heparinized glass test tube. In 15 patients, capillary sampling was chosen for practical reasons. Since venous and capillary samples give similar results, the data are presented together [37].

The blood sample was immediately put into ice water and centrifuged within 60 min. Plasma was then removed and stored at -70°C until analysis.

Patient data (body weight, length, actual dose administered), as well as exact times for start and stop of doxorubicin infusion, and for blood sampling, were noted. Serum concentrations of creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), determined before the administration of doxorubicin, were also recorded.

Analytical Procedure

Doxorubicin and doxorubicinol were assayed by an analytical procedure based on reversed-phase liquid chromatography with fluorometric detection [18]. They were all processed in the Karolinska Pharmacy, Stockholm.

Briefly, 100 µl of plasma sample was mixed with the internal standard (daunorubicin) dissolved in 0.1 M phosphoric acid and transferred into a SepPak C18 extraction

TABLE I. Baseline Data and Pharmacokinetic Parameters of Children > 1-Year-Old

	All patients > 1 year of age	Dose 37–43 mg/m^2	Dose < 37 or > 43 mg/m^2
No. of patients	107	95	12
Female:male ratio	44:63	40:55	4:8
Age in years	4.7 (1.3–17.5)	4.9 (1.3–17.5)	4.6 (1.5–13.3)
BMI	16.3 (12.6–25.6)	16.4 (12.8–25.6)	15.8 (12.6–20.4)
BSA (m^2)	0.75 (0.5–1.9)	0.75 (0.5–1.9)	0.74 (0.5–1.3)
WBC count, 10^9/L	12.8 (0.8–307)	12.4 (0.8–307)	7.6 (2.5–54)
Doxorubicin dose (mg/m^2)	39.6 (18.3–46.6)	39.7 (37–42.2)	32.7 (18.3–46.6)
Doxorubicin conc. (ng/ml) (observed)	61.6 (22–360)	60.6 (22–271)	75.5 (34–360)
Doxorubicin conc. (ng/ml) (dose normalized)	62.8 (22.6–334)	60.5 (22.6–272)	76.6 (41.4–334)
CV%	64.8	57.2	74.2
Doxorubicinol conc. (ng/ml) (dose normalized)	7.5 (0–59.9)	7.5 (0–59.9)	6.3 (2.2–20.6)
CV%	89.4	91.5	74.2
Doxorubicionol/Doxorubicin (%)	12.7 (0–80.6)	12.9 (0–80.6)	7.0 (3.7–19.0)
Doxorubicin plasma clearance (ml/min/m^2)	411 (77–1143)	427 (95–1143)	339 (77–624)
CV %	45.8	44.3	53.4

Median values and range (in brackets) are given. For some parameters, the coefficient of variation percent (CV%) is also presented, calculated as SD/mean × 100.
BMI = Body Mass Index; BSA = Body Surface Area; WBC = White Blood Cell.

column (Waters Inc., Milford, MA). After rinsing with 5 ml of phosphate buffer (pH 7.0), the anthracyclines were eluted with 4 ml of methanol. The eluate was evaporated, redissolved in 0.1 M phosphoric acid and injected into a Nova-Pak Phenyl Radial-Pak Cartridge (Waters Inc.). Acetonitrile, typically 40%, in 0.01 M phosphoric acid was used as mobile phase. Minor adjustments of the acetonitrile concentration in the mobile phase were sometimes necessary to maintain optimal chromatographic resolution of the anthracyclines. The fluorometric detector (Shimadzu Model RF-551 Spectrofluorometric Detector, Shimadzu Corporation, Kyoto, Japan) was operated at 501/600 nm.

The detection limit of doxorubicin and doxorubicinol was 0.2 ng/ml. All plasma concentrations reported are mean values of duplicate analyses. The precision of the analytical procedure (coefficient of variation) was 2.2% (intra-day) and 3.4% (inter-day).

Pharmacokinetic Evaluation and Statistics

A limited sampling model for plasma level monitoring was used [16]. Plasma concentrations of doxorubicin and doxorubicinol were measured 23 hr after the start of a 24-hr doxorubicin infusion.

Since the dose of doxorubicin actually administered sometimes differed from the target dose, the observed doxorubicin and doxorubicinol concentrations were normalized for a dose of 40 mg/m^2 by the formula:

$$\frac{\text{Observed concentration} \times \text{target dose}}{\text{actual dose}}$$

Based on protocol data for body weight and length we calculated the patient's BSA by the formula [19]:

$$m^2 = \sqrt{\frac{\text{height(cm)} \times \text{weight(kg)}}{3600}}$$

BMI was calculated as weight/(height)^2. Plasma clearance (Cl) was calculated according to the formula Cl = D/T/Css, where D/T is the actual dose rate and Css is the observed steady state concentration of the drug. It has been shown that about 93% of the steady state concentration of doxorubicin is reached after 23 hr of infusion [16], and this was compensated for in the calculations of plasma clearance by dividing the observed 23 hr doxorubicin concentration with 0.93.

The Spearman rank test (two-sided) was used to examine correlations, the Mann-Whitney U test to compare values from two groups, and the Kruskall–Wallis test to examine differences between three or more groups. A multivariate linear model was constructed, after a natural log transformation of doxorubicin concentration values and white blood cell (WBC) counts, and a collapse of age into three groups. Residual normality plots showed that the assumptions of linear models were met. The SPSS 10.0 software package (SPSS Inc. Chicago, IL) was used for the calculations. $P < 0.05$ was considered as statistically significant.

RESULTS

Children (> 1 year)

The dose actually administered ranged between 18.3–46.6 mg/m^2, with a median dose of 39.6 mg/m^2. Most of the patients, however, received a dose close to the target dose of 40 mg/m^2. Out of 107, 95 children received

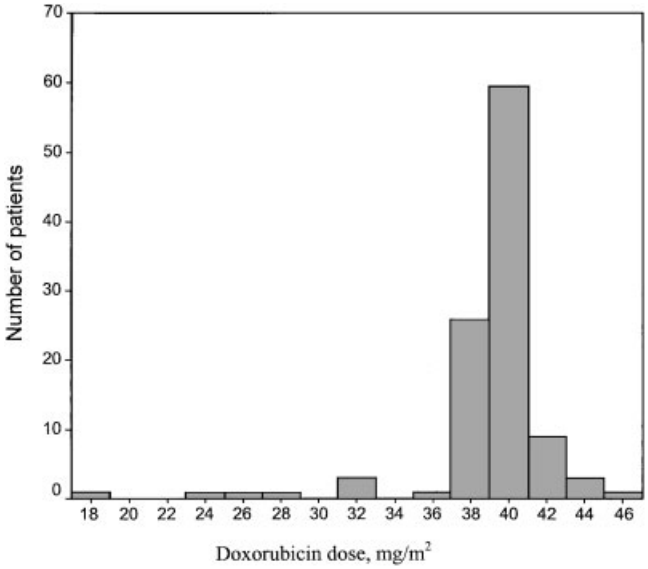

Fig. 1. Range of doxorubicin doses administered and the number of patients receiving each dose.

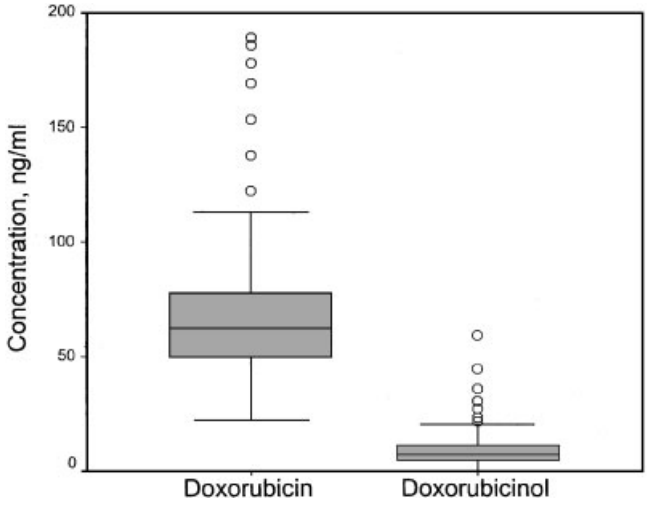

Fig. 2. Plasma concentrations of doxorubicin and doxorubicinol in children > 1-year-old, normalized for a dose of 40 mg/m^2. Plasma samples were drawn 23 hr after the start of a 24 hr doxorubicin infusion on Day 1 of the induction treatment. The box-and-whisker plot shows median, and 1st and 3rd quartiles; whiskers extend to the highest and lowest value, excluding outliers, which are denoted by circles. Doxorubicin plasma concentrations > 200 ng/ml are not shown in the figure, but are included in the calculations (n = 3; 234, 272, and 334 ng/ml, respectively).

between 37 and 43 mg/m^2 of doxorubicin (Fig. 1). Pharmacokinetic parameters for all 107 patients > 1 year, as well as for the subset of children who received 37–43 mg/m^2 of doxorubicin, are presented in Table I. Obviously, there were only minor differences. In the following, data for the whole group are presented, if not otherwise stated.

After normalization for a dose of 40 mg/m^2, the median plasma concentration of doxorubicin was 62.8 ng /ml, range 22.6–334 ng/ml (Fig. 2). The 10th and the 90th percentile values were 36.8 and 115 ng/ml, respectively. Three patients had values above 200 ng/ml. The clinical files of these three patients were retrospectively examined; no serious side-effects or complications influencing further therapy were registered.

The median plasma clearance was 411 ml/min/m^2, and the 10th and 90th percentile values 225 and 701 ml/min/m^2, respectively.

There was no significant difference in the doxorubicin concentration of patients from the six centers participating in the study. The median doxorubicin level was very similar in boys and girls, 62.8 ng/ml and 63.0 ng/ml, respectively.

The doxorubicin concentration differed significantly between age groups ($P = 0.003$). Children aged 4–6 years had the highest median doxorubicin concentration, 77.9 ng/ml (Fig. 3), followed by children aged 2–4 years, median 64.3 ng/ml. Both 1–2-year-old and > 6 year old children had median values of about 50 ng/ml.

Serum creatinine increased significantly with age as expected ($P < 0.001$), while there was no correlation between age and AST or ALT. Neither AST, ALT nor creatinine correlated significantly with doxorubicin concentrations. Patients with clearly elevated AST and ALT values, here defined as levels > 3 times normal (n = 8 and n = 7, respectively), were compared with patients having values below this cut-off. The median doxorubicin concentrations were similar: 62 and 66 ng/ml for patients with high and low ALT values,

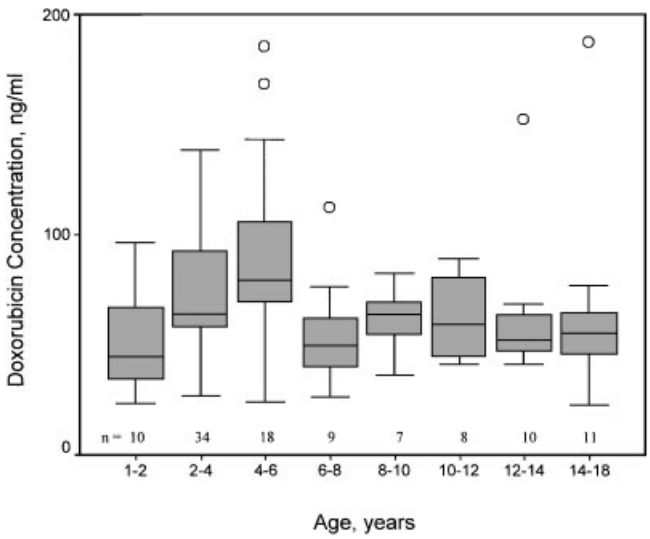

Fig. 3. Plasma concentrations of doxorubicin, normalized for a dose of 40 mg/m^2, in relation to age.

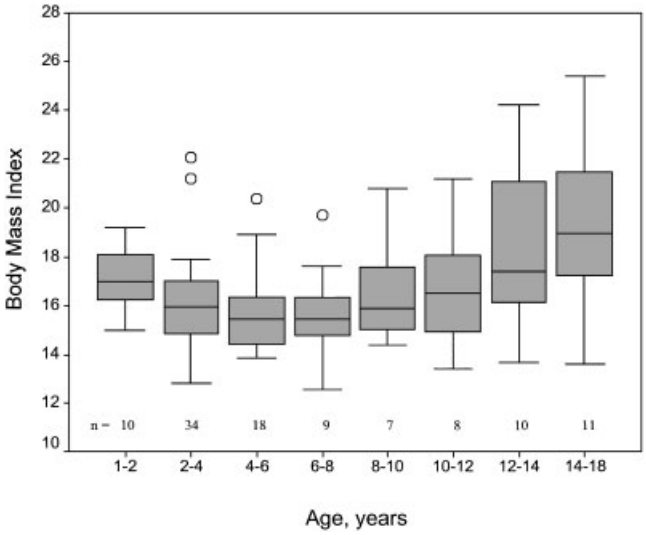

Fig. 4. BMI in relation to age.

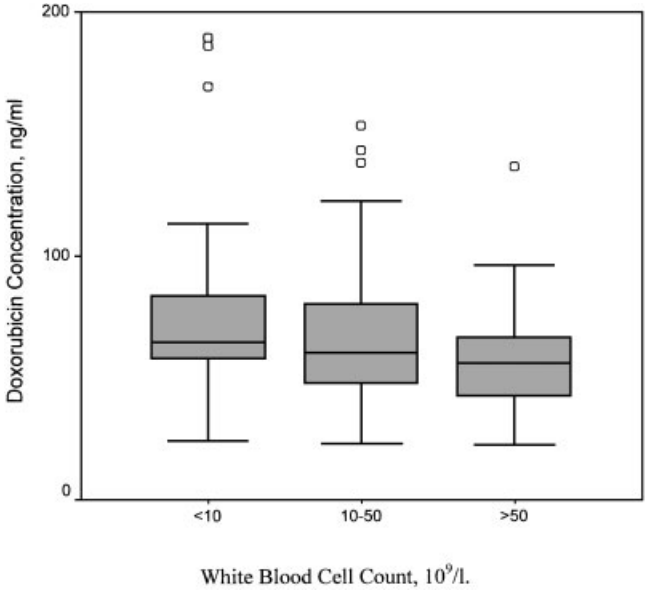

Fig. 5. Dose normalized plasma concentrations of doxorubicin in relation to WBC count in peripheral blood at diagnosis. Cut-off values for WBC counts are those used for risk classification in the NOPHO ALL-92 protocol.

and 63 and 64 ng/ml for patients with high and low AST values, respectively.

BMI differed significantly between age groups ($P = 0.009$). Children aged 4–6 years had the lowest BMI (Fig. 4). There was no statistically significant correlation between BMI and doxorubicin concentration.

In the NOPHO ALL-92 protocol, WBC counts of < 10, 10–50, or $> 50 \times 10^9$/L at diagnosis are criteria for standard, intermediate, and HR, respectively. When patients were grouped according to these cut-off values, there was a significant difference in doxorubicin concentrations between the groups ($P = 0.015$); post-hoc tests showed that only the highest and lowest groups differed significantly. The lowest plasma concentration, median 55.3 ng/ml, was found in the group with WBC counts, > 50 and the highest, median 64.4 ng/ml, in the group with WBC counts, $< 10 \times 10^9$/L (Fig. 5). The correlation between individual WBC values and doxorubicin concentrations did not reach statistical significance ($P = 0.052$; correlation coefficient -0.19). WBC counts did not differ significantly between age groups ($P = 0.058$), but the WBC counts tended to be lower in the 2–4 and 4–6-year-old children than in the other age groups (not shown).

To sort out whether age influenced the plasma concentrations of doxorubicin, after adjusting for WBC count and/or BMI, a multivariate linear model was constructed. Data of the 95 children, who had received doxorubicin doses between 37–43 mg/m^2, were used, after age had been collapsed into three groups: 1–2, 2–6, and > 6 years. The influence of age on doxorubicin pharmacokinetics remained significant: $P = 0.028$ for age 1–2 years, and $P = 0.011$ for age > 6 years, when compared with the reference group of 2–6-year-old children. The influence of WBC count and BMI was not significant in this model, $P = 0.08$ and $P = 0.12$, respectively. The predictive value of the model was fairly low, $R^2 = 0.17$.

The median plasma concentration of the metabolite doxorubicinol was 7.5 ng/ml, range 0–59.9 ng/ml, after normalization for a doxorubicin dose of 40 mg/m^2 (Fig. 2). High doxorubicinol concentrations were found in patients with high doxorubicin levels ($P < 0.001$; correlation coefficient 0.42). The median value for the doxorubicinol/doxorubicin quotient was 0.13, range 0–0.81. There was no correlation between doxorubicinol concentrations and age, gender, serum aminotransferases, serum creatinine or WBC count.

Infants

All five infants studied received doses < 40 mg/m^2, and the youngest ones received the lowest doses (Table II). With the doses chosen, the observed plasma concentrations of doxorubicin were similar in all five infants, with a range of 43.5–59.5 ng/ml. This is slightly lower than the observed median concentration of 61.6 ng/ml in children > 1 year. The 3 months old infant had a considerably lower plasma clearance (181 ml/min/m^2) than the 7–9 months old infants, whose clearance values of 350–431 ml/min/m^2 were similar to those of children > 1 year. The doxorubicinol concentrations varied between 0 and 9.8 ng/ml, without any obvious correlation to age (Table II).

TABLE II. Pharmacokinetic Data on Five Infants < 1 Year of Age

Sex	Age (months)	Weight (kg)	Length (cm)	BSA (m^2)	Dose (mg/m^2)	Doxorubicin conc.		Plasma clearance of Doxorubicin ($ml/min\,m^{-2}$)	Doxorubicinol conc.
						Observed ng/ml	Dose normalized ng/ml		Dose normalized (ng/ml)
M	3	5.8	59	0.31	12.2	43.5	143.0	181	0.0
F	7	6.6	63	0.34	32.4	59.5	73.5	352	9.8
M	7	7.8	70	0.39	28.2	52.1	73.8	350	0.0
F	7	9.2	73	0.43	27.7	46.2	66.7	387	3.2
F	9	9.3	70	0.43	37.6	56.4	60.0	431	4.9

BSA = Body surface area.

DISCUSSION

Most patients received doxorubicin in amounts close to the target dose of the treatment protocol. Minor deviations might be due to the use of a nomogram rather than an exact formula to calculate the BSA of the patients. The reason for significant dose reduction in individual cases is not known to us.

To be able to include all patients in the pharmacokinetic calculations, we normalized the observed doxorubicin and doxorubicinol concentrations for a dose of 40 mg/m^2. Studies in adults have shown that the pharmacokinetics of doxorubicin are linear, at least within the dose range 22–60 mg/m^2 [4].

The plasma concentrations of doxorubicin ranged widely between patients, 22.6–334 ng/ml, even after dose normalization. Three patients differed markedly from the others with plasma levels above 200 ng/ml. The possibility that extreme values may be caused by technical errors, e.g., in the sampling procedure, must always be considered. The fact that the three patients with the highest plasma concentrations did not have any severe side-effects registered in their files might support this idea. On the other hand, previous studies in adults have also shown about ten-fold differences in plasma concentrations of doxorubicin [2–4], and our retrospective analysis of side-effects may not give the true picture, since the NOPHO ALL-92 protocol does not include any systematic registration of side-effects.

The median plasma clearance in children >1 year found here is similar to that of adults [2,3], but somewhat lower than what has previously been reported for children [14,20].

In adults, a lower plasma clearance of doxorubicin has been observed in females as compared to males [21]. It has also been reported that nausea associated with anthracycline-containing regimens is more severe in girls than in boys [22], and that girls run a higher risk of abnormalities in cardiac function [23,24]. We did not find any differences in doxorubicin pharmacokinetics between boys and girls that could explain these gender differences in side-effects. Eksborg et al. [15], who studied 31 children with ALL, reported similar findings.

There was no significant correlation between serum creatinine and the plasma concentration of doxorubicin in the present study, an expected finding, since only about 10% of the drug is excreted by the kidneys [20]. Doxorubicin is eliminated mainly by the liver, and it has been suggested that patients with elevated aminotransferases and/or bilirubin should receive reduced doses of the drug [20]. Neither AST nor ALT values correlated significantly to plasma concentrations of doxorubicin in our patient material. A small number of children had elevated aminotransferase values, but their doxorubicin levels did not differ from those of other

children. The NOPHO ALL-92 protocol does not recommend dose adjustments based on aminotransferase levels, and our data support this strategy, at least in children without serious liver function disturbances.

Published data regarding the age dependency of doxorubicin pharmacokinetics in children are equivocal. McLeod et al. [14] observed a lower clearance, normalized for BSA, in children younger than 2 years as compared to children aged 2–20 years, while weight-normalized clearance did not differ in the two age groups. In contrast, Crom et al. [20] found that plasma clearance of doxorubicin, normalized to BSA, was not related to age, but clearance normalized to weight was higher in patients below the median age of 10.5 years than in older children. Eksborg et al. [16] did not find a clear correlation between age and pharmacokinetics, but an influence of age could not be excluded since the plasma levels of doxorubicin, after dose normalization based on BSA, were higher in children below 5.4 years than in older children. One reason for the diverging data in previous studies is probably that they contain relatively few patients, especially in the lowest age groups.

In the present study, we found that children aged 4–6 years, had the highest steady state plasma concentrations of doxorubicin among children > 1 year, followed by 2–4-year-old children. Age contributed significantly to the variability in pharmacokinetics also after adjusting for WBC and BMI. Since the median doxorubicin concentration in 4–6-year-old children was about 50% higher than in 1–2 and > 6 year old children, it is reasonable to believe that this difference might be of clinical importance. The physiological basis for the influence of age is not clear, however.

Body composition has been discussed as an important variable in the pharmacokinetics of antineoplastic drugs [25], even though relatively little attention has been paid to this fact when optimizing drug treatment. In a study of the pharmacokinetics of 6-mercaptopurine in children with ALL, it was found that the AUC values increased with decreasing weight/height percentile, an index of the fat body mass [26]. Data on the importance of body composition on anthracycline pharmcokinetics in adults are conflicting [27,28]. Eksborg et al. [15] could not establish any significant correlation between doxorubicin pharmacokinetics and BMI in children, but noted a trend to higher plasma levels in patients with low BMI.

In our patients, BMI varied with age as expected from normative data [29], with the lowest BMI in the 4–6-year-old group of children, i.e., the patients who had the highest doxorubicin levels. There was no significant correlation between individual BMI values and doxorubicin concentrations, however. Still we cannot rule out that the current dosing based on BSA was of some importance for the high doxorubicin concentrations in the relatively slender children in the 4–6-year-old group.

There is an extensive uptake of doxorubicin into nucleated blood cells, as well as into tissues [3,30,31]. Therefore, we thought it was of interest to see if plasma concentrations of the drug correlated to the WBC count at diagnosis, with the hypothesis that a high number of nucleated blood cells might influence the plasma concentration. When patients were grouped according to the WBC count (< 10, 10–50, and $> 50 \times 10^9$/L, respectively), there was indeed a significant difference, with the lowest doxorubicin concentration in the group with the highest WBC count. The difference between the groups was modest, however, less than 20%. In the multivariate model, the contribution of WBC count to pharmacokinetic variability did not reach statistical significance.

Very little data on the pharmacokinetics of doxorubicin has been reported for individuals < 1 year of age. McLeod et al. [14] found a trend toward a lower rate of systemic clearance based on BSA in four infants, 0.17–0.83 years old. Our limited data indicate that infants > 6 months of age have plasma clearance similar to that of children > 1 year old, and that dose reduction not is necessary from a strictly pharmacokinetic point of view. For infants < 6 months of age, dose reduction is recommended in most protocols [14], and our single observation in a 3 months old infant is in accordance with this strategy.

Doxorubicinol is the only cytotoxic metabolite of doxorubicin [33]. The in vitro toxicity of doxorubicinol has been reported to be similar to [34] or lower [33,35] than that of doxorubicin, but the influence of the metabolite on the therapeutic effect and the side-effects after doxorubicin administration is unknown. Some data suggest that doxorubicinol might contribute to the cardiotoxicity seen after treatment with doxorubicin [36]. Since the median doxorubicinol/doxorubicin quotient was 0.13, our findings indicate that doxorubicinol generally adds little to the therapeutic effect in children. A few patients had a considerably higher quotient, however, and in these cases doxorubicinol could be of some importance.

Doxorubicin might be a candidate for therapeutic monitoring by plasma level determinations, if it can be established that the individual variability in plasma levels from course to course is low (or changes in a predictable way) and that there is a statistically significant relationship between plasma levels and outcome or toxicity. A relationship between plasma concentrations of doxorubicin and the outcome of remission induction therapy has been reported for acute nonlymphocytic leukemia in adults [32], but we are not aware of any study of the correlation between doxorubicin plasma levels and therapeutic effect in childhood leukemia (or any other pediatric malignancy). One reason for the lack of such data is that anthracyclines generally are used in combination therapy. We have not yet attempted to make a correlation between plasma concentration and effect, since the observation time is still short for many of our

patients. Even when the final outcome is known, it is unlikely that any correlation between plasma concentration and relapse rate can be established without studying a larger patient population, since the expected relapse rate is low and the use of many other cytotoxic drugs in the treatment protocol will act as a confounding factor. The intra- and inter-patient variability of anthracyclines are the subject of two ongoing studies of children with hematological malignancies and solid tumors, where we also intend to study the influence of concomitant medications.

CONCLUSIONS

In our opinion, the present data do not justify modifications of the dose regimen currently used, which is based on BSA. It is intriguing, however, that the age groups with the highest doxorubicin concentrations, (2-) 4–6-year-old children, also make up a large proportion of SR ALL cases with good prognosis. If further studies show a similar relationship to age, and/or an influence of BMI, there might be a case for dose adjustment based on such parameters. The relationship between plasma concentration of cytotoxic drugs and tumor burden at diagnosis also deserves further study.

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