Cancer Chemother Pharmacol (1999) 44: 203–209

ORIGINAL ARTICLE

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Vincristine pharmacokinetics after repetitive dosing in children

Received: 11 September 1998 / Accepted: 5 February 1999

Abstract *Purpose*: We studied vincristine disposition after 169 weekly i.v. bolus injections in 32 children with acute lymphoblastic leukemia, non-Hodgkin lymphoma, or Wilms' tumor. The aim of the study was to determine intrapatient and interpatient variability in vincristine disposition and demographic, clinical, and biochemical characteristics influencing this variability. *Methods*: Vincristine plasma concentrations were measured by a high-performance liquid chromatography assay with electrochemical detection. A limited sampling strategy was used based on a bayesian parameter estimation algorithm that is part of the ADAPT II software package. A two-compartment, first-order model was fitted to the data, and pharmacokinetic parameters were calculated from the model using the ADAPT II software. For statistical analysis, analysis of variance (ANOVA), *t* test, simple and multiple regression analysis, and non-parametric or robust equivalents were used. *Results*: Results showed a large intrapatient and interpatient variability in distribution half-life, elimination half-life, total body clearance, apparent volume of distribution at steady state, and area under the concentration–time curve. Intrapatient variability was significantly smaller than interpatient variability for all these parameters except distribution half-life. The diagnosis or treatment protocol turned out to be the most predictive characteristic; leukemia and non-Hodgkin lymphoma patients had a significantly higher total body clearance than Wilms' tumor patients. *Conclusions*: We conclude that both intrapatient and interpatient variability in vincristine pharmacokinetics is large in pediatric cancer patients and that variability, although significantly influenced by diagnosis, largely remains unpredictable.

Key words Vincristine · Pharmacokinetics · Repetitive dosing · Children

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Introduction

Pharmacokinetic studies on vincristine, an antimitotic drug widely used in pediatric oncology, are scarce [1, 5, 8, 20, 22, 30, 31, 35]. Thus recommendations for vincristine dosing schedules, including dose adjustments for young children and capping of the dose in older children, are based on empiricism and tradition rather than on pharmacokinetic data. Not surprisingly, these recommendations have recently been challenged [19, 29]. Furthermore, the scarcity of pharmacokinetic data has limited the feasibility of studies on the correlation of pharmacokinetics and (cyto)toxicity, studies that are needed to optimize treatment.

One reason for the limited knowledge of vincristine pharmacokinetics is the lack of specific and sensitive analytical methods to measure vincristine concentrations in biological fluids until a decade ago. Before that time, nonspecific methods, such as tritium-labeled vincristine and radioimmunoassay, were used. Although studies using nonspecific methods provided useful information on tissue uptake and elimination routes, results concerning vincristine concentrations had to be interpreted with caution because not only the parent drug vincristine, but also active or inactive metabolites might be measured [1, 15, 16, 21, 22, 30, 31, 35]. At the end of the 1980s, the introduction of a specific high-performance liquid chromatography (HPLC) method, sufficiently sensitive for clinical use even in children, made appropriate pharmacokinetic studies of vincristine possible and was a stimulus for new interest in the field [2, 9, 24, 37].

The few HPLC-based studies on vincristine pharmacokinetics in children showed a large interpatient variability [5, 8]. However, data on intrapatient variability are still nonexistent and are needed before pharmacokinetic/pharmacodynamic relations during repetitive dosing can be explored and rational dosage regimens can be designed. For example, if we know that intrapatient variability is small and a correlation is found between systemic exposure and (cyto)toxicity, we might be able to identify patients at risk for treatment failure or severe toxicity and thus individualize dosing.

Factors contributing to the variability in vincristine pharmacokinetics are largely unknown. Crom and De Graaf mentioned age and concomitantly administered medication as factors possibly related to vincristine pharmacokinetics [5, 8]. Other demographic, clinical, and biochemical characteristics have been studied, but data are inconclusive [10, 11, 23, 25, 30, 35].

The aims of this study are therefore to determine intrapatient variability in vincristine pharmacokinetics in children after repetitive dosing and to evaluate demographic, clinical, and biochemical characteristics influencing variability of vincristine disposition.

Materials and methods

Patients

Newly diagnosed children admitted to our hospital with acute lymphoblastic leukemia (ALL), T-cell non-Hodgkin lymphoma (NHL) stage III/IV, or Wilms' tumor were eligible for the study. Patients were enrolled between November 1994 and November 1996. The study was approved by the Ethics Committee of the University Hospital Groningen, and enrolment of patients took place only after written informed consent had been obtained. Patients with ALL or NHL were treated according to the Dutch Childhood Leukemia Study Group (DCLSG) protocol ALL-8 (a BFM-based protocol) [26]. Only patients treated according to the ALL-8 standard-risk group (SRG) or medium-risk group (MRG) were enrolled, while high-risk patients were excluded because their postinduction treatment was distinctly different. Patients with Wilms' tumor were treated according to the National Wilms' Tumor Study Protocol IV (NWTS IV) [13].

All patients received repetitive weekly vincristine injections. In protocol ALL-8, four vincristine injections were administered during induction therapy (weeks 1–4 from the beginning of treatment), and four injections during consolidation (weeks 17–20 in ALL-8 SRG and weeks 23–26 in ALL-8 MRG). In the Wilms' tumor protocol, vincristine was administered weekly from the first week of treatment for at least 8 weeks. Vincristine dosage was 1.5 mg/m^2 administered as an i.v. bolus injection (15 s, at a maximum of 2.0 mg, except for the first four administrations in protocol ALL-8, where the maximum was 2.5 mg. Vincristine was administered according to body weight (0.05 mg/kg) instead of body surface area in all children younger than 1 year and in children below 30-kg body weight, who were treated according to NWTS IV regimens.

Concomitantly administered antileukemic medication in protocol ALL-8 included prednisolone, dexamethasone, daunorubicin, doxorubicin, l-asparaginase, and intrathecal methotrexate, cytarabine, and prednisolone. In the NWTS IV protocol, concomitantly administered cytostatic agents included dactinomycin and doxorubicin. Standard supportive medication included cotrimoxazol and bisacodyl in both treatment protocols.

Body weight and height, liver and kidney function parameters, total plasma protein and albumin concentration, and platelet count were monitored in all patients. The glomerular filtration rate was estimated as follows: 49 × (height in cm)/serum kreatinin in μM/l. Incidental medication administered on the same day as vincristine was also registered.

Pharmacokinetic studies

The plan of investigation was to obtain a series of blood samples after each of the first eight vincristine administrations. Samples were taken through an intravenous line. The sample site was different from the injection site to avoid falsely high vincristine concentrations due to adsorption of vincristine to the injection line. The sample schedule was limited to six samples at t = 0, 10, 30, 90, and 240 min after the start of the vincristine injection, and a final sample was taken after 600 or 1200 min, depending on logistics. This schedule was designed using the optimal sampling design module of the ADAPT II software package, based on the primary pharmacokinetic parameters of 17 previously studied patients [6, 8]. Blood samples of 2 ml each were collected in heparinized tubes and immediately put on ice. After centrifuging the blood at 4 °C and 800 g for 10 min, plasma was separated and stored at −80 °C until analysis.

The vincristine plasma concentration was measured by HPLC with electrochemical detection [2]. The sensitivity of the HPLC method was 0.5 ng/ml. Coefficients of variation at a concentration of 0.5 ng/ml and 15 ng/ml were 2.1% and 1.6% in within-day precision studies and 5.2% and 0.4% in between-days studies, respectively.

A two-compartment, first-order model was fitted to the data. Primary pharmacokinetic parameters were estimated by iteration using the ADAPT II parameter estimation software and maximum a posteriori bayesian algorithm [7]. As prior for the bayesian analysis, we used primary pharmacokinetic parameters of the previously mentioned patients, in whom an extended sampling schedule and a weighted least-squares parameter estimation strategy were used. Parameters of the variance model were fixed, with a constant coefficient of variation across the concentration range (σ, 0.1; γ, 2.0). Secondary pharmacokinetic parameters such as distribution half-life ($t_{1/2a}$), elimination half-life ($t_{1/2b}$), total body clearance (CL), apparent volume of distribution at steady state (V_{dss}), and area under the concentration–time curve (AUC) were calculated from the model.

Statistical analysis

Parametric tests were used. Because the distribution of pharmacokinetic parameters did not appear to be completely normal, nonparametric or robust parametric methods were used to confirm the significance of the results. Intrapatient and interpatient variability were compared by variance analysis using ANOVA, and results were checked by the Kruskal-Wallis method.

To identify significant relationships between pharmacokinetic parameters and demographic, clinical, and biochemical variables, the t test and simple linear regression were used. Thereafter, significant variables were analyzed in multiple and stepwise regression analysis. The Mann-Whitney test and least-absolute deviates were used to check the results.

The software packages used for statistical analysis were Statview 4.1 for Apple and Systat 5.02 for DOS.

Results

Of 43 patients eligible for inclusion, no informed consent was obtained in eight and no pharmacokinetic studies could be done in three because blood sampling was not possible, resulting in 32 evaluable patients. Twenty-five

Table 1 Summary of patient and clinical characteristics

Age (years)	Median, 4.6 (range, 0–16)
Sex (M/F) (*n*)	19/13
Treatment protocol (ALL-8/NWTS IV) (*n*)	26/6
Vincristine dosage (≥1.3 mg/m^2/< 1.3 mg/m^2) (*n*)	146/23

patients had ALL, one NHL, and six Wilms' tumor. Table 1 summarizes the characteristics of the patients enrolled in the study. Pharmacokinetic studies were done after 169 vincristine administrations. Vincristine dosage was significantly lower (< 1.3 mg/m^2) than the standard dosage of 1.5 mg/m^2 in some children due to capping of the dose at 2.0 or 2.5 mg, dosage calculation according to body weight instead of body surface area, or dose reduction because of unacceptable toxicity.

Intrapatient variability and interpatient variability in pharmacokinetic parameters were large. Figure 1 shows variability in total body clearance, elimination half-life, and apparent volume of distribution. A summary of secondary pharmacokinetic parameters is given in Table 2. Variance analysis showed a significantly smaller intrapatient variability compared to interpatient variability with regard to elimination half-life, total body clearance, apparent volume of distribution, and AUC (ANOVA and Kruskal-Wallis, $P \leq 0.01$), whereas no significant difference was found for distribution half-life (Table 3).

Monovariate analysis of demographic, clinical, and biochemical variables with the *t* test and Mann-Whitney test or simple linear regression showed that diagnosis, standard co-treatment with anthracyclines, kidney function, age, and incidental coadministration of captopril significantly influenced clearance (expressed in ml/min per m^2). Vincristine administration rank number, sex, dosage per m^2, total bilirubine and alkaline phosphatase level, total protein or albumin level, and platelet count did not have a significant influence on vincristine clearance. Similarly, coadministration of ondansetron, cephalosporines, and macrolides did not show a significant influence on vincristine clearance (Table 4).

In multiple and stepwise regression analysis, only the influence of diagnosis on vincristine clearance remained significant (Table 5). Similar results were found when data were analyzed with least absolute deviates regression analysis. A significantly higher clearance was found in ALL/NHL patients than in Wilms' tumor patients (mean, 381 ± 140 vs. 258 ± 120 ml/min per m^2; $P = 0.0092$; Fig. 2).

To be able to compare the results of this study with the results of other investigators, we analyzed the influence of age on vincristine clearance in ALL patients separately. Clearance was expressed in ml/min per m^2 and in ml/min per kg. We found a weak positive correlation (simple linear regression: regression coefficient, 0.005; $P = 0.038$; $r^2 = 0.031$) if clearance was expressed in ml/min per m^2, and a weak inverse correlation

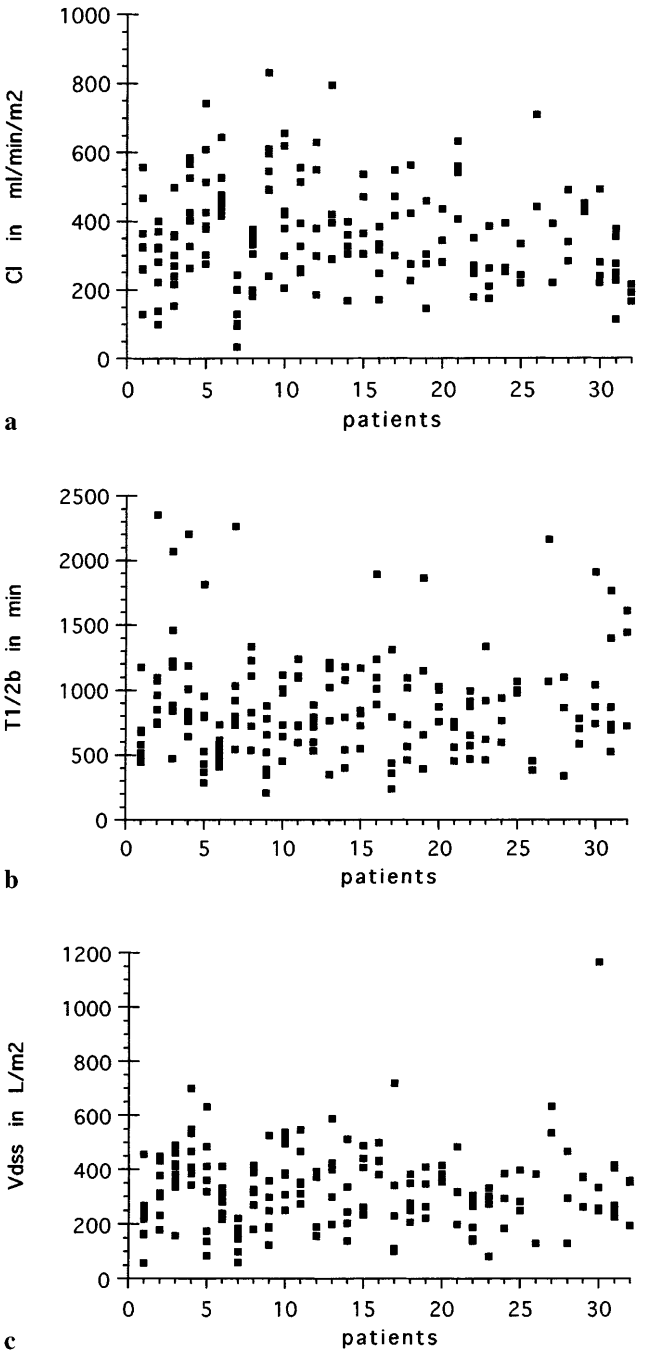

Fig. 1 Variability in **a** total body clearance (*CL*), **b** elimination half-life ($t_{1/2b}$), and **c** volume of distribution (V_{dss}) after 169 vincristine administrations

(simple linear regression: regression coefficient, 1.951E-4; $P = 0.033$; $r^2 = 0.033$) if clearance was expressed in ml/min per kg (Fig. 3).

Discussion

Our results show that both intrapatient and interpatient variability in vincristine pharmacokinetics in pediatric cancer patients is large, as previously described for

Table 2 Summary of secondary pharmacokinetic parameters following 169 vincristine injections

	Mean	SD	Median	Minimum	Maximum
$t_{1/2a}$ (min)	7.6	2.3	7.2	3.7	15.9
$t_{1/2b}$ (min)	864	402	792	206	2352
Cl (ml/min per m^2)	357	146	333	34	830
V_{dss} (l/m^2)	325	144	318	56	1165
AUC (mg/l × min)	5.0	3.9	4.2	1.5	45.1

$t_{1/2a}$, distribution half-life; $t_{1/2b}$, elimination half-life; Cl, total body clearance; V_{dss}, volume of distribution at steady state; AUC, area under the concentration–time curve

Table 3 Summary of analysis of variance (ANOVA) for intrapatient and interpatient variance in pharmacokinetic parameters

Parameter	Mean square		*P*
	Intrapatient	Interpatient	
$t_{1/2a}$ (min)	5.35	5.37	0.47
$t_{1/2b}$ (min)	141410	250846	0.01[a]
Cl (ml/min per m^2)	0.01	0.05	< 0.0001[a]
V_{dss} (l/m^2)	17266	36420	0.002[a]
AUC (mg/l × min)	11.77	31.8	< 0.0001[a]

$t_{1/2a}$, distribution half-life; $t_{1/2b}$, elimination half-life; Cl, total body clearance; V_{dss}, apparent volume of distribution at steady state; AUC, area under the concentration–time curve
[a] Significant

anticancer drugs but generally not for other drugs [36]. Diagnosis appears to be the most important variable influencing vincristine disposition among the demographic, clinical, and biochemical variables investigated.

Intrapatient variability of total body clearance, elimination half-life, apparent volume of distribution, and AUC was significantly smaller than interpatient variability. No difference was found between intrapatient and interpatient variability in distribution half-life. Although intrapatient variability was smaller than interpatient variability, the ratio of intrapatient to interpatient variability for vincristine disposition was much larger than for most drugs [27]. This implies that, even when vincristine disposition following one dose has been defined in an individual patient, it will remain virtually impossible to predict what the disposition will be following the next dose.

Although our data show a large variability in pharmacokinetics, there is no reason to doubt their reliability. The HPLC assay used has been well validated and proven to be highly accurate, as pointed out in the "Materials and methods" section. Pharmacokinetic data analysis using bayesian analysis is a widely accepted and reliable method that can overcome potential problems of a limited sampling strategy [17, 28, 32]. Only practical problems related to the collection of blood through small peripheral lines in young patients may have limited the accuracy of the estimated distribution half-life. The

Table 5 Influence of demographic, clinical, and biochemical variables on vincristine clearance in multiple regression analysis

Variable	Direction of influence on clearance	*P*
Diagnosis	ALL/NHL > Wilms	0.0092[a]
Age		0.0948
GFR		0.4279
Anthracyclines		0.5677
Captopril		0.8525

GFR, glomerular filtration rate; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma
[a] Significant

Table 4 Monovariate analysis of the influence of demographic, clinical, and biochemical variables on clearance

Variable	Direction of influence on cl (ml/min per m^2)	*P*	Test
Vincristine administration rank number		0.56	ANOVA
Sex		0.46	*t* test
Diagnosis	ALL/NHL > Wilms	< 0.0001	*t* test/Mann-Whitney test
Age	Positive	0.014	Linear regression analysis
Dosage/m^2		0.54	Linear regression analysis
Total bilirubine		0.64	Linear regression analysis
Alkaline phosphatase		0.78	Linear regression analysis
GFR	Positive	0.047	Linear regression analysis
Total protein		0.31	Linear regression analysis
Albumin		0.051	Linear regression analysis
Platelets		0.11	Linear regression analysis
Anthracyclines	+ > −	≤0.01	*t* test/Mann-Whitneyy test
Ondansetron		0.08	*t* test
Cephalosporines		0.08	*t* test
Macrolides		0.06	*t* test
Captopril	+ < −	< 0.05	*t* test/Mann-Whitney test

GFR, glomerular filtration rate; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma; ANOVA, analysis of variance

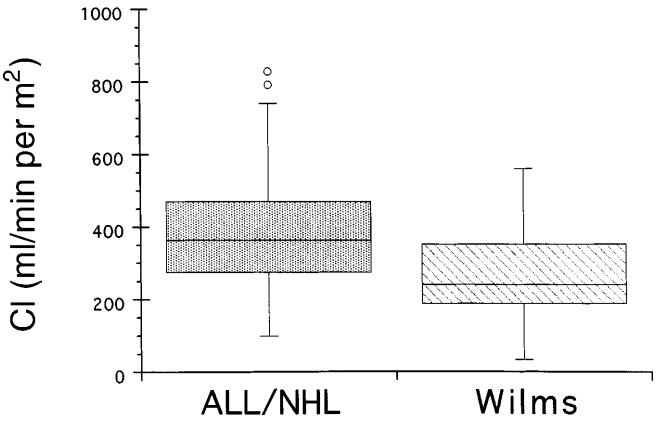

Fig. 2 Influence of diagnosis on vincristine clearance in acute lymphoblastic leukemia (*ALL*) and non-Hodgkin lymphoma (*NHL*) patients ($n = 137$) and in Wilms' tumor patients ($n = 32$)

high variability in vincristine disposition therefore appears to be real, with some caution as far as distribution half-life is concerned.

Diagnosis was the only statistically significant factor influencing clearance in multivariate analysis; total body clearance was larger in ALL patients, including the one NHL patient, than in Wilms' tumor patients. For a better understanding of the apparent influence of diagnosis, we should consider a number of other variables that could contribute to the effect of diagnosis. ALL and Wilms' tumor patients were significantly different with respect to comedication, kidney function, age, platelet count, and dosage of vincristine per m^2 when all vincristine administrations studied were considered (data not shown).

Steroids were the only comedication consistently different in the two diagnosis groups; leukemia patients always received steroids with vincristine, whereas Wilms' tumor patients never did. Steroids could therefore be accountable for the difference in vincristine disposition. Several mechanisms could play a role. First, steroids may induce hepatic cytochrome P450 3A isoenzymes [4]. It has been suggested that vincristine is a substrate for these enzymes [14, 38, 39]. Thus, steroids may increase the biotransformation and clearance of vincristine by enzyme induction [18]. Second, steroids themselves may act as substrates for P450 3A [12]. Consequently, a competition between steroids and vincristine for the P450 3A enzymes could result in a decreased biotransformation and clearance of vincristine [34]. Furthermore, steroids may act as multidrug resistance (MDR) modulators [33]. Inhibition of the P glycoprotein efflux pump by steroids might result in a decreased vincristine clearance due to an increase in cellular accumulation and a decrease in P glycoprotein-dependent biliary elimination. Thus the apparent influence of diagnosis on vincristine disposition might very well be due to steroids. Several mechanisms with opposing effects might be active. The precise role of steroids in the metabolic elimination of vincristine requires further investigation. If steroids play a role, the impact of P450 induction apparently outweighs the other steroid effects.

Kidney function, age of the patient, anthracycline comedication, platelet count, and dosage per m^2 could also be relevant factors in the influence of diagnosis on vincristine disposition based on theoretical grounds, as argued by other authors or former observations [1, 5, 8, 23, 30, 35, 38, 39]. However, in multivariate and stepwise analysis, only the influence of diagnosis retained its significance. Obviously, the tumor itself could be a factor in the variability of vincristine distribution and clearance, but we were unable to find any evidence to support this idea.

Some of our patients received incidental comedication, such as macrolides, ondansetron, captopril, and cephalosporines that can interact with either the hepatic cytochrome P450 system or with P glycoprotein [33, 34]. No statistically significant effect of any of these drugs on vincristine disposition was found in multiple regression analysis.

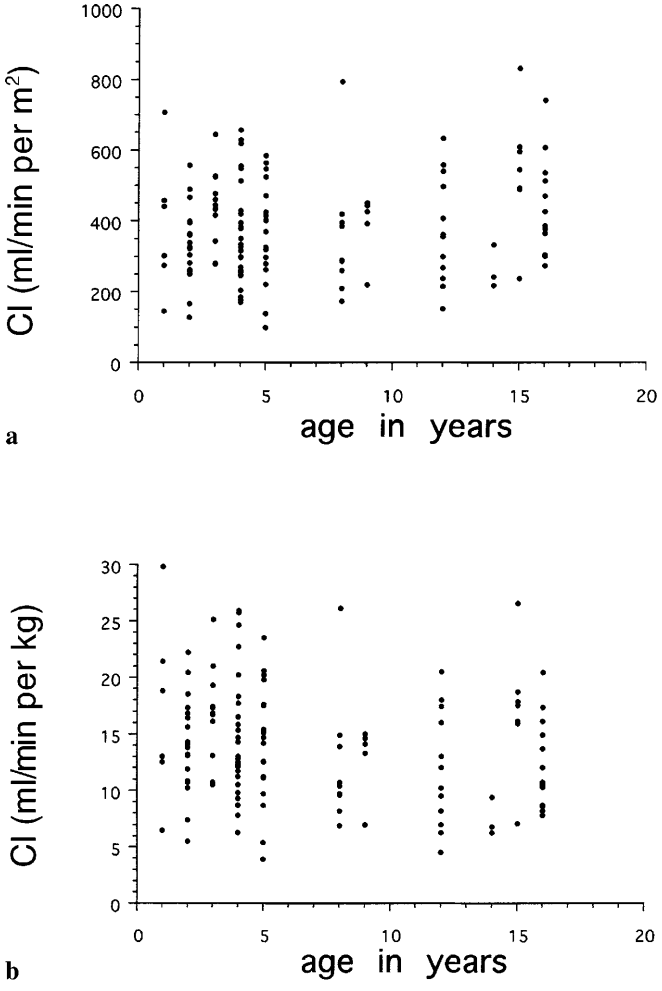

Fig. 3a,b Influence of age on vincristine clearance in acute lymphoblastic leukemia (*ALL*) patients. Clearance is expressed in **a** ml/min per m^2 and **b** ml/min per kg

Although diagnosis turned out to be a significant predictor of vincristine disposition, a major part of the variability in vincristine disposition remains unaccounted for. Genetical polymorphism of the hepatic cytochrome P450 family could be a factor [3].

We confirmed the observation by Crom et al. [5] that vincristine clearance in infants under 1 year is lower than in older children. Beyond 1 year, these investigators found a weak negative correlation between age and vincristine clearance, whereas we only found a weak negative correlation if clearance was expressed in ml/min per kg; when it was expressed in ml/min per m^2, we found a weak positive correlation. Interpatient variability was large in both studies, and a definite conclusion regarding the effect of age above 1 year on clearance is therefore not possible in either study.

To our knowledge, this study is the largest pharmacokinetic study on vincristine that has been published to date. Nevertheless, we were unable to confirm a number of previously reported observations. Although we found a positive correlation between dosage per m^2 and AUC, we were unable to confirm a significant correlation between dosage per m^2 and elimination half-life, as found by other investigators [23, 35]. In addition, our data did not show a positive correlation between AUC and serum alkaline phosphatase [10, 35] or between AUC and serum bilirubin concentration, another measure of obstructive liver dysfunction. Our data did not show a negative correlation between platelet count and AUC, as reported by Sethi et al. [30]. Ratain et al. [25], described a positive correlation between albumin level and vinblastine clearance. We were unable to show this correlation for vincristine. Because vincristine binds to globulins rather than to albumin, we also evaluated whether total serum protein concentration was correlated to clearance, but we did not find this correlation either [11].

Differences between our results and those of others may at least in part be attributed to different assays for the measurement of vincristine in plasma. We used a specific HPLC assay, in contrast to some other investigators, who used a radioimmunoassay. Furthermore, our patient population was relatively homogeneous with regard to dosage per m^2 and serum alkaline phosphatase, bilirubin, albumin, and protein concentrations. Thus our inability to confirm the previously reported influence of these variables on vincristine disposition might be due to a limited sensitivity of the study in this respect.

In conclusion, both intrapatient and interpatient variability of vincristine pharmacokinetics was wide and largely unexplained. Diagnosis is the only variable significantly influencing clearance, possibly due to the influence of steroids. Individualization of vincristine therapy based on pharmacokinetics after a single injection will not be feasible. Moreover, for a study on the relationship between cumulative systemic vincristine exposure and long-term toxicity, it will be necessary to collect pharmacokinetic data after each of the subsequent vincristine administrations. The relatively low vincristine clearance in infants supports the traditional lower dosing in these patients. In our pediatric population, we did not find decreased vincristine clearance in older patients. Thus there is no convincing pharmacokinetic basis for capping the dose at 2.0 or 2.5 mg/m^2.

Acknowledgements We would like to thank Dr. M. Wilkinson for his advise in statistics and H. Tenk for technical assistance.

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