

Pharmacokinetics of Vincristine Monotherapy in Childhood Acute Lymphoblastic Leukemia

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ABSTRACT

We studied vincristine pharmacokinetics in 70 children newly diagnosed with acute lymphoblastic leukemia, after a single dose of vincristine as monotherapy. Vincristine plasma concentrations were measured by HPLC analysis. A two-compartment, first-order pharmacokinetic model was fitted to the data by maximum *a posteriori* parameter estimation. In this group of children pharmacokinetic factors were highly variable: median (25th and 75th percentiles) total body clearance, 228 (128–360) mL·min⁻¹·m⁻²; elimination half-life, 1001 (737–1325) min; apparent volume of distribution at steady state 262 (158–469) L/m². Vincristine clearance was substantially slower than has been reported previously for children receiving vincristine in combination with steroids as part of combination chemotherapy (median clearance, 228 mL·min⁻¹·m⁻² versus mean clearance, 381 and 482 mL·min⁻¹·m⁻², respectively). Steroids are known as inducers of vincristine-metabolizing cytochrome P₄₅₀ 3A4

enzymes. The absence of steroids during our study appears to be the most likely explanation for this difference. Furthermore, we found that vincristine clearance was faster in patients with hyperdiploid (>50 chromosomes) than in patients with diploid or hyperdiploid (46–50 chromosomes) leukemic blasts. (*Pediatr Res* 52: 113–118, 2002)

Abbreviations

ALL, acute lymphoblastic leukemia
CYP 3A4, cytochrome P₄₅₀ 3A4
DCLSG, Dutch Childhood Leukemia Study Group
CL, total body clearance
AUC, area under the concentration-time curve
Vd_{ss}, apparent volume of distribution at steady state
t_{1/2α}, distribution half-life
t_{1/2β}, elimination half-life

Vincristine, one of the naturally occurring vinca alkaloids extracted from the leaves of the periwinkle plant *Catharanthus roseus*, continues to play a key role in the treatment of childhood ALL since its introduction in 1962 (1). Vincristine exerts an antimetabolic effect (2–4) and induces apoptosis in various hematologic cell lines (5–8). Its antileukemic effect *in vivo* is determined by both variability in exposure of the leukemic cells and variability in sensitivity of the cells to the effect of vincristine. *In vitro* sensitivity of leukemic cells has been well studied (9), but the variability in exposure of leukemic cells *in vivo* has received less attention. Therefore, we studied vincristine pharmacokinetics in children newly diagnosed with ALL, after a single dose of vincristine.

Vincristine-induced cell kill in a human lymphoblastic leukemia cell line was proportional to saturation of cellular binding sites (10), suggesting that the concentration of vincristine to which the cell is exposed is an important determinant of the antileukemic effect of vincristine. *In vitro*, vincristine accumulates in cells to concentrations as high as 500 times extracellular concentrations and is slowly released from the cells after restoration in drug-free medium (11, 12). Tissue distribution of vincristine was studied with ³H-labeled vincristine in the rat and revealed accumulation in spleen, adrenal and thyroid glands, large and small intestines, heart, lung, kidney, liver, and marrow. Penetration in rat eye, fat, and brain tissue and in human cerebrospinal fluid appears to be very poor (13–15).

The first pharmacokinetic studies on vincristine in man were performed when ³H-labeled vincristine became available, 15 y after the introduction of vincristine in clinical practice. It was found that urinary excretion accounts for up to 12% of excreted radioactivity (16, 17). The biliary system appeared to be the principal route of excretion (13, 18–20). Recent studies dem-

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onstrated that vincristine is at least partially metabolized by CYP 3A4 enzymes (21–24).

The development of an HPLC method for the measurement of vincristine concentrations in biologic fluids made it possible to study vincristine pharmacokinetics with greater specificity than the previously used RIA (25–28). CL appeared to be faster in children than in adults (mean CL, 431 and 189 mL·min⁻¹·m⁻², respectively) (29, 30). Both intra- and inter-patient variability turned out to be large in pediatric cancer patients (31).

In each of these studies, vincristine was administered in combination with other cytotoxic drugs or corticosteroids. The possibility of drug interactions with respect to both pharmacokinetics and pharmacodynamics should therefore be considered. To appreciate the effect of comedication on vincristine pharmacokinetics, a description of the pharmacokinetics of vincristine as a monotherapy is required. Therefore, we undertook a study of vincristine pharmacokinetics after a bolus injection of vincristine in a group of children newly diagnosed with ALL, receiving no other cytotoxic drugs or corticosteroids, during an up-front window study. We will describe the influence of demographic and biochemical variables and coadministered noncytotoxic drugs on the variability of pharmacokinetics of vincristine as a single cytotoxic drug in these children.

METHODS

Patients. Children newly diagnosed with ALL were asked to participate in an up-front window study of vincristine pharmacokinetics before the start of standard induction chemotherapy according to DCLSG protocol ALL-9. The diagnosis was confirmed by the central laboratory of the DCLSG, using conventional cytologic and immunologic criteria (32–34). Exclusion criteria for the ALL-9 protocol were the following: age older than 18 y, treatment with corticosteroids or cytotoxic drugs in a period of 4 wk before diagnosis, ALL as second malignancy, relapsed ALL, or mature B-cell leukemia. Children with meningeal involvement at diagnosis were eligible for the ALL-9 protocol, but did not participate in the window study. Patients were enrolled between June 1997 and January 2000 in 10 participating hospitals cooperating in the DCLSG. Demographic and prognostic variables of all patients were registered at the DCLSG central office. Biochemical measurements and comedication during the window study were registered locally by the treating physicians.

The study protocol was approved by the Medical Ethics Review Board of the participating hospitals, and written informed consent was obtained from all patients or parents.

Study design. At the start of the study, 1.5 mg/m² vincristine was administered as an i.v. bolus injection. Blood sampling was scheduled before and 10, 30, 180, and 1440 min after vincristine administration. This schedule was designed with the optimal sampling design module of the ADAPT II software package (Biomedical Simulations Resource, University of Southern California, Los Angeles, CA, U.S.A.) (30, 35). Heparinized blood samples (4 mL) were drawn from a different site from the vincristine injection and immediately placed on ice. The actual time of vincristine injection and blood sampling was

registered. Plasma was separated within 3 h after sampling by centrifugation of the blood at 4°C and 560 × g for 10 min, and plasma was stored at –80°C until analysis. The study ended after 3 d when standard combination induction therapy was started. Corticosteroids or other cytotoxic drugs were not administered during the time of the study.

HPLC analysis of vincristine. Vincristine plasma concentration was measured by HPLC with electrochemical detection (28). The sensitivity of the assay was 0.48 μg/L, and coefficients of variation were 6.2% (0.48 μg/L) and 4.2% (18.40 μg/L) in within-day precision studies, and 10.3% (0.48 μg/L) and 8.5% (18.40 μg/L) in between-day studies. Plasma samples from all participating hospitals were measured at the Department of Pharmacy and Toxicology of the University Hospital Groningen.

Pharmacokinetic data analysis. A two-compartment, first-order pharmacokinetic model was fitted to the vincristine concentration data. Primary pharmacokinetic variables were estimated by maximum *a posteriori* parameter estimation with a Bayesian algorithm using the ADAPT II software package with priors from 32 previously studied patients (30, 31, 35, 36). Factors of the variance model were fixed at a coefficient of 0.1 and an exponent of 2.0. Secondary pharmacokinetic variables such as CL, AUC, Vd_{ss}, t_{1/2 α}, and t_{1/2 β} were calculated from the model.

Statistical analysis. Nonparametric methods were used because the distribution of pharmacokinetic variables did not appear to be normal. The Spearman rank test was used to detect significant correlations. When patients could be assigned to one of two different groups, the Mann-Whitney *U* test was used, and when three or more groups could be distinguished, the Kruskal-Wallis test was used, with correction for multiple comparisons according to Duncan. The software package used for statistical analysis was SPSS version 9.0 for Windows (Chicago, IL, U.S.A.).

RESULTS

Of 78 patients enrolled in the study, eight were not evaluable for pharmacokinetic analysis for the following reasons. HPLC analysis was impossible in one patient because of high background voltage in all plasma samples, which made comparison with the calibration curve impossible. In one patient blood samples were drawn from the vincristine injection site, resulting in falsely high vincristine concentrations. In one patient blood samples were contaminated with infusion fluid, resulting in falsely low vincristine concentrations. In five patients plasma sample tubes were lost, thawed, or damaged during transport. Table 1 summarizes characteristics of the remaining 70 evaluable patients. Children younger than 1 y of age were not represented in the study group. Among the evaluable patients were relatively few patients with T-cell ALL and pseudodiploid blast cell cytogenetics, in comparison to patients with newly diagnosed ALL in general. Patients with diploid blast cell cytogenetics were more frequent in the study population.

Results of pharmacokinetic data analysis are shown in Table 2. Even in this group of children, which were all newly diagnosed

Table 1. Characteristics of evaluable patients

	Number of patients	%
Age (y)		
<1	0	0
1	5	7
2–5	34	49
6–9	12	17
10–16	19	27
Sex		
M	38	54
F	32	46
Risk group		
NHR	52	74
HR	18	26
WBC ($\times 10^9/L$)		
<10	35	50
10–50	24	34
>50	11	16
Platelets* ($\times 10^9/L$)		
<20	19	27
20–99	30	43
≥ 100	19	27
FAB morphology		
L1	53	76
L2	17	24
Immunophenotype*		
c-ALL	41	59
pre-B ALL	18	26
T-ALL	8	11
pro-B ALL	1	1
Cytogenetics**		
diploid	14	20
hypodiploid	5	7
pseudodiploid	12	17
hyperdiploid (46–50)	8	11
hyperdiploid (>50)	16	23
DNA index*		
<1.16	52	74
≥ 1.16	16	23

* 2 cases unknown; ** 15 cases unknown.

Table 2. Summary of vincristine secondary pharmacokinetic variables in 70 children newly diagnosed with ALL

	Median	Interquartile range
CL ($mL \cdot min^{-1} \cdot m^{-2}$)	228	128–360
AUC ($mg \cdot L^{-1} \cdot min^{-1}$)	6.7	4.2–12.3
$t_{1/2 \alpha}$ (min)	6.6	6.1–7.5
$t_{1/2 \beta}$ (min)	1001	737–1325
Vd_{ss} (L/m^2)	262	158–469

with ALL and receiving vincristine as a monotherapy, interpatient variability of secondary pharmacokinetic variables such as CL, $t_{1/2 \beta}$, and Vd_{ss} was substantial (Fig. 1). Two patients received a smaller vincristine dosage than the standard dosage of 1.5 mg/m² owing to capping of the dose at 2.5 mg.

Univariate analysis showed that vincristine clearance was correlated with the biochemical measures for alkaline phosphatase ($n = 53$; $r = -0.31$; $p = 0.025$; Fig. 2A) and gamma-glutamyltransferase ($n = 33$; $r = -0.42$; $p = 0.016$; Fig. 2B), but not with other biochemical measurements such as aspartate aminotransferase ($n = 57$), alanine aminotransferase ($n = 58$), albumin ($n = 48$), total protein ($n = 42$), bilirubin (n

= 30), urea nitrogen ($n = 57$), and creatinine ($n = 58$), neither with age at diagnosis, weight, height, body surface area, nor sex. The numbers in parentheses indicate the numbers of patients for whom that specific measurement was available for statistical analysis. Plasma concentrations for the biochemical variables were within the physiologic range or slightly increased, limiting the possibility to detect correlations with pharmacokinetic factors. $t_{1/2 \alpha}$ was correlated with conjugated bilirubin concentration ($n = 21$; $r = -0.49$; $p = 0.023$).

Vincristine clearance was also correlated with cytogenetics of leukemic cells (Kruskal-Wallis, $n = 55$, $p = 0.008$). Analysis after correction for multiple comparisons according to Duncan revealed that CL in children with hyperdiploid (>50 chromosomes) blasts was faster than in children with diploid or hyperdiploid (46–50 chromosomes) blasts ($p < 0.05$; Fig. 3). The difference in CL was not associated with differences in alkaline phosphatase or gamma-glutamyltransferase concentrations between these groups of patients. CL and $t_{1/2 \beta}$ were not significantly correlated to measurements of leukemic cell load such as percentage of blast cells in bone marrow or peripheral blood, white blood cell count, or number of platelets in peripheral blood. Neither were immunophenotype ($n = 52$), liver, spleen, lymph node, or mediastinal enlargement, nor performance status at diagnosis correlated to clearance of vincristine. $t_{1/2 \alpha}$ was correlated with number of platelets ($n = 70$; $r = 0.49$; $p < 0.001$).

Although no other cytotoxic drugs or steroids were given during the window study, individual patients received other systemically acting drugs such as allopurinol, cephalosporins, co-trimoxazole, furosemide, paracetamol, and vancomycin. In children receiving cephalosporins ($n = 15$), $t_{1/2 \beta}$ was significantly smaller than in children who did not receive cephalosporins ($n = 33$; median, 737.9 versus 1069 min; $p = 0.036$; Fig. 4). Consistent with this observation, median CL was faster in patients receiving cephalosporins, although not statistically different (median, 266.5 versus 184.2 $mL \cdot min^{-1} \cdot m^{-2}$; $p = 0.085$). The difference in CL between patients who did and who did not receive cephalosporins was not associated with differences in alkaline phosphatase concentration or gamma-glutamyltransferase concentration. However, an association between cephalosporin comedication and hyperdiploid (>50 chromosomes) blast cell cytogenetics was suspected ($p = 0.066$). CL was not significantly different in children who were treated with allopurinol ($n = 30$), co-trimoxazole ($n = 6$), furosemide ($n = 7$), paracetamol ($n = 10$), or vancomycin ($n = 6$), compared with children who were not treated with these drugs. Considering the numbers of patients treated with co-trimoxazole, furosemide, and vancomycin, an interaction of these drugs with vincristine pharmacokinetics might be difficult to detect in this group of patients.

DISCUSSION

We studied the disposition of vincristine given as a monotherapy to children newly diagnosed with ALL, and possible correlations of pharmacokinetic factors with clinical and biochemical variables. We found that vincristine pharmacokinetic factors are highly variable, even in this relatively homogeneous

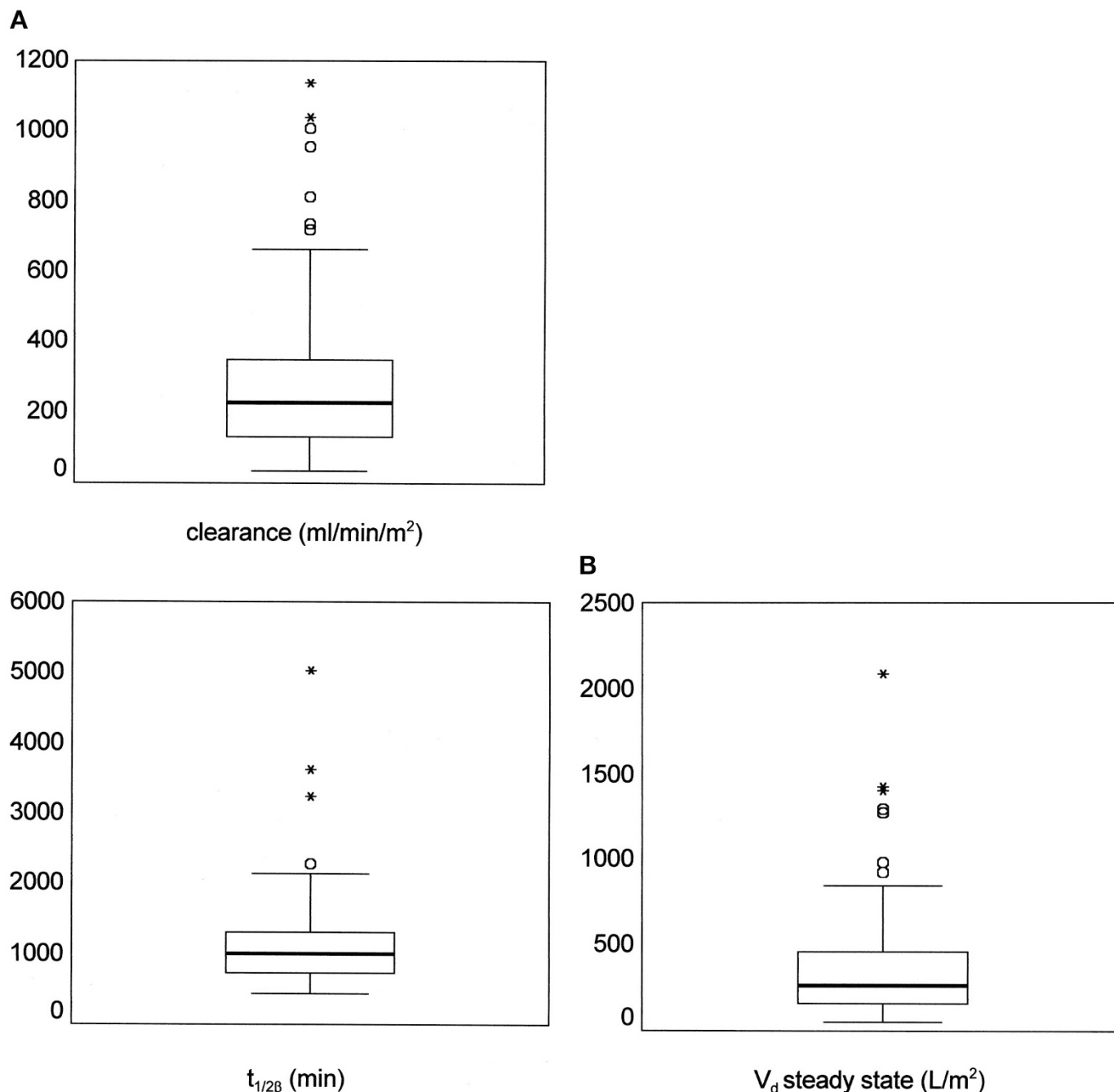


Figure 1. Vincristine pharmacokinetic variability. Box plots of vincristine CL, $t_{1/2\beta}$, and $V_{d_{ss}}$ illustrate vincristine pharmacokinetic variability in 70 children newly diagnosed with acute lymphoblastic leukemia.

group of patients. This means that leukemic blasts in individual patients are exposed to highly variable concentrations of vincristine during variable periods of time. At this point, it is uncertain whether such variability in drug exposure results in a similar variability in antileukemic effect.

We confirmed that vincristine disposition in children is characterized by a long terminal $t_{1/2\beta}$ and a large $V_{d_{ss}}$, as has been reported in adults (16, 17, 37, 38). A long $t_{1/2\beta}$ and a large $V_{d_{ss}}$ suggest avid tissue binding.

CL in our patients was slower than has previously been reported for children with ALL (Table 3) (29, 31). A possible explanation for this observation could be the in-

duction of vincristine-metabolizing enzymes by comedication, administered during combination chemotherapy but not during our up-front window study of vincristine as a monotherapy. Prednisone and dexamethasone are inducers of CYP 3A4 (39, 40) and were part of combination chemotherapy regimens in the earlier studies of vincristine pharmacokinetics in ALL patients. The CYP 3A4 enzymes play a role in vincristine metabolism (22, 23, 41–43). Steroids may have caused CYP 3A4 induction and increased vincristine metabolism, leading to faster CL. This hypothesis is supported by the fact that CL in Wilms' tumor patients, who did not receive steroids, was similar to the CL in our ALL

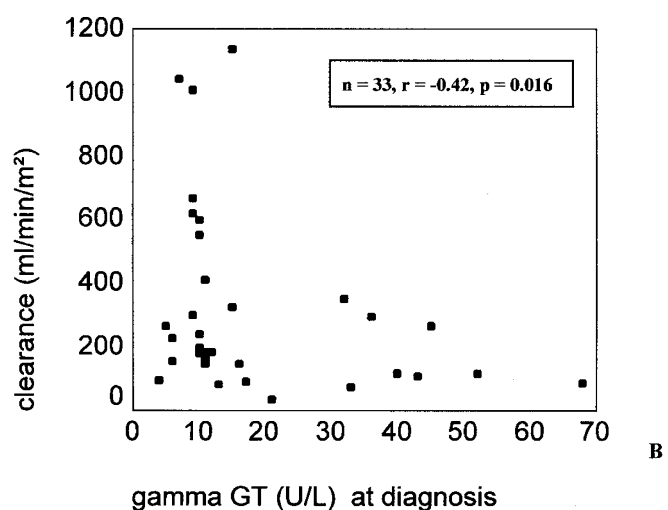
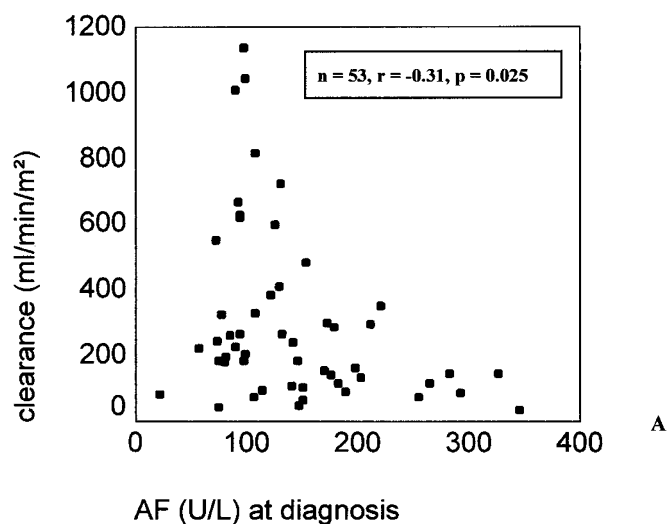


Figure 2. Vincristine CL and biochemical measurements. Correlation between vincristine CL and alkaline phosphatase (AF) concentration (A) and gamma-glutamyltransferase (gamma-GT) concentration (B).

patients (31). (Table 3) Obviously, further studies would be appropriate to confirm the suggested effect of steroids on the pharmacokinetics of vincristine.

The question arises whether vincristine dose should be adjusted in case of comedication with drugs that have been proven to interfere with vincristine pharmacokinetics. The aim of such a dose adjustment would be to achieve a target exposure of leukemic cells. However, individualized dosing is only rational if there is evidence that achieving a certain vincristine target exposure leads to a better response or less toxicity. At this time, such evidence is not available for vincristine.

Vincristine CL turned out to be inversely related with alkaline phosphatase and gamma-glutamyltransferase concentrations, which is consistent with an earlier report in adult cancer patients (37). An increase of the plasma concentration of these biochemical factors reflects a lower biliary elimination. The correlation between increased alkaline phosphatase plasma concentration and a reduced vincristine clearance could be

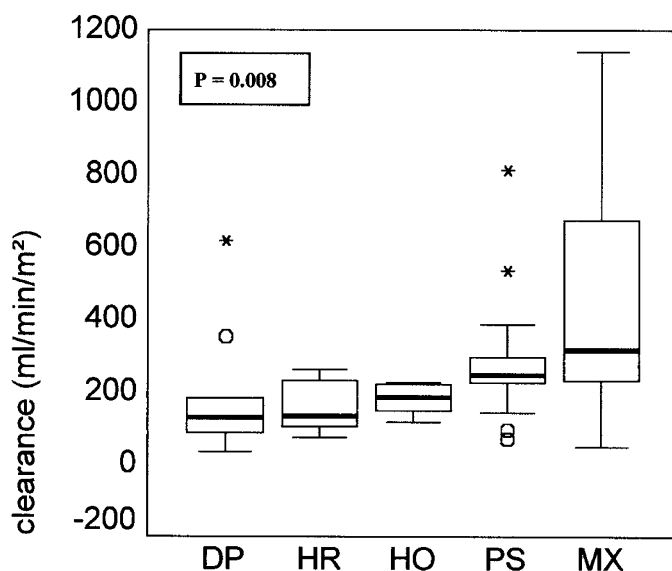


Figure 3. Blast cell cytogenetics and vincristine CL. Difference in CL between children with different blast cytogenetics. HR, hyperdiploid (46–50 chromosomes); HO, hypodiploid; PS, pseudodiploid; MX, hyperdiploid (>50 chromosomes); DP, diploid. *p* value from Kruskal-Wallis analysis.

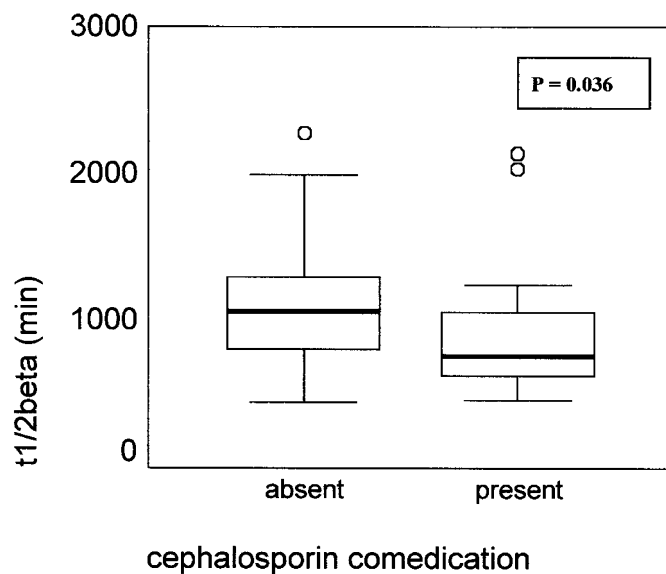


Figure 4. Influence of cephalosporin comedication on vincristine pharmacokinetics. Box plots of vincristine $t_{1/2\beta}$ in the absence or presence of cephalosporins.

detected, even when alkaline phosphatase concentrations were within the normal range in our patients. We conclude that vincristine pharmacokinetic variability is partially determined by biliary elimination rate, within the physiologic range.

CL was faster in patients with hyperdiploid (>50 chromosomes) than in patients with diploid or hyperdiploid (46–50 chromosomes) blasts. A faster vincristine clearance, and consequently a smaller vincristine exposure, in the hyperdiploid (>50 chromosomes) patients seems to be in contrast with the favorable prognosis in this group. More information about the relation between vincristine pharmacokinetics, pharmacodynamics, and pharmacogenomics, and about the possible association between hyperdiploid (>50 chromosomes) blast cell

Table 3. Comparison of vincristine CL with previously reported values

	CL (mL·min ⁻¹ ·m ⁻²)		
	Median	Interquartile range	
		95% Confidence interval	
Groninger	228	128–360	
		Mean	SD
Gidding (Wilms') 31	258	120	18–498
Gidding (ALL) 31	381	140	101–661
Crom 29	482.4	342.0	–201.6–1166.4

cytogenetics and cephalosporin comedication, is necessary to understand this apparent contradiction.

In conclusion, we found that pharmacokinetics of vincristine monotherapy in a group of children, newly diagnosed with ALL, is highly variable. In comparison with previously published data, our results suggest that comedication is an important factor influencing vincristine elimination rate. Further studies are needed to answer the question of whether dose adjustments on the basis of comedication should be considered.

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