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ORIGINAL ARTICLE

Population pharmacokinetics and pharmacogenetics of vincristine in paediatric patients treated for solid tumour diseases

Romain Guilhaumou · Nicolas Simon · Sylvie Quaranta · Arnauld Verschuur · Bruno Lacarelle · Nicolas Andre · Caroline Solas

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Abstract
Purpose The interindividual variability of vincristine pharmacokinetics is quite large, but the origins of this variability are not properly understood. The aim of this study was to develop a population pharmacokinetic model of vincristine in a paediatric population treated for solid tumour disease and evaluate the impact of different *ABCB1*, *CYP3A4* and *CYP3A5* polymorphisms on the different pharmacokinetic parameters.
Methods We assessed vincristine pharmacokinetics in 26 children treated for various solid tumour diseases. Genotypes were determined by real-time PCR with a LightCycler™ and *ABCB1* haplotypes calculated using the software program Phase 2.1. Vincristine plasma concentrations were determined by LC–MS/MS, and a population approach was performed on 184 samples by the NONMEM computer program. Demographic, therapeutic and genotypic covariables were evaluated on vincristine pharmacokinetic parameters.
Results The frequency of *CYP3A4*1A/*1A* and **1A/*1B* genotypes were 87.5 and 12.5%, respectively. *CYP3A5*1/*3* and **3/*3* were observed in 20.8 and 79.2% of the patients, respectively. The three major haplotypes were (allelic frequencies) CGC (50%), CGT (14.6%) and TTT (23.2%). Vincristine pharmacokinetics was well described by a two-compartment model. Large interindividual and interoccasion variability were observed. The different polymorphisms studied did not improve the model prediction.
Conclusions *CYP3A4*, *CYP3A5* and *ABCB1* polymorphisms did not significantly affect in vivo vincristine pharmacokinetics. Our results demonstrate that vincristine pharmacokinetic variability cannot be explained by these genetic polymorphisms.

Keywords Vincristine · Pharmacogenetics · Population pharmacokinetics · Paediatric · Solid tumours

R. Guilhaumou · B. Lacarelle · N. Andre · C. Solas
Inserm U911, Faculté de Pharmacie,
27 Boulevard Jean Moulin, 13385 Marseille Cedex 5, France

R. Guilhaumou · S. Quaranta · B. Lacarelle · C. Solas
Laboratoire de Pharmacocinétique et Toxicologie,
Hôpital de la Timone, 264 rue Saint Pierre,
13385 Marseille Cedex 5, France

N. Simon
Laboratoire de Pharmacologie Médicale et Clinique,
Hôpital de la Timone, 264 rue Saint Pierre,
13385 Marseille Cedex 5, France

A. Verschuur · N. Andre
Service d'Oncologie Pédiatrique,
Hôpital de la Timone, 264 rue Saint Pierre,
13385 Marseille Cedex 5, France

Introduction

Vincristine, a natural vinca alkaloid derived from *Catharanthus roseus*, is a widely used and effective drug in paediatric oncology. Vincristine plays a pivotal role in the treatment of paediatric acute lymphoblastic leukaemia (ALL), but it is also used in the management of Hodgkin's and non-Hodgkin's lymphomas, rhabdomyosarcoma, neuroblastoma and Wilms tumour [1].

Vincristine pharmacokinetics is characterized by a large interpatient variability [1–3], which can be explained by its physicochemical properties and an important metabolism. In vitro studies on vincristine have demonstrated a metabolism through the cytochrome P450 (CYP450) system in the

liver, particularly by the CYP3A4 and CYP3A5 isoforms, and transport by the P-glycoprotein (encoded by the *ABCB1* gene) [4, 5]. CYP3A-mediated metabolism of vincristine was supported by the observation of clinical drug–drug interactions with itraconazole and nifedipine, leading to an increase in neurotoxicity [6–8]. This suggests that high concentrations of vincristine through the inhibition of CYP3A may increase the risk of neurotoxicity. Therefore, the variability of CYP3A might impact both the pharmacokinetics and the toxicity of vincristine.

It has been reported that genetic polymorphisms of metabolizing enzymes and drug transporters could be involved in pharmacokinetic variability [9]. The frequency of these different polymorphisms varies according to race. Pollock et al. [10] observed an interracial difference in the survival of childhood lymphoblastic leukaemia, and Renbarger et al. [11] reported an effect of race on vincristine-associated neurotoxicity in paediatric ALL patients. In these studies, African-American children with ALL had lower survival and neurotoxicity which may be related to a difference in CYP3A activity. Moreover, an influence of CYP3A5 expression in human hepatocytes has been described on vincristine metabolism in vitro [12]. Consequently, the pharmacokinetic variability of vincristine could be explained by genetic differences affecting the metabolism and/or the distribution of the drug. Single-nucleotide polymorphisms (SNPs) in the *ABCB1* gene have been described, C1236T in exon 12, G2677T(A) in exon 21 and C3435T in exon 26, being the most commonly studied in the literature [13, 14]. These SNPs have been found to be associated with altered P-gp expression and function. Several SNPs have also been identified for *CYP3A4* and *CYP3A5* genes [15]. The *CYP3A4*1B* and *CYP3A5*3* alleles are associated with a decrease or an absence of the enzyme activity, leading to a clearance increase, as already demonstrated for immunosuppressive drugs [16]. All of these SNPs could be involved in the pharmacokinetic variability of vincristine and could also explain the variability observed in vincristine-induced neurotoxicity.

The aim of this study was therefore to determine vincristine pharmacokinetic parameters in paediatric patients with solid tumour diseases and evaluate the impact of different ABCB1, CYP3A4 and CYP3A5 polymorphisms on vincristine pharmacokinetics.

Patients and methods

Patients

Twenty-six children, treated in the paediatric cancer unit of the Timone University Hospital for various solid tumour diseases, were included in this study. The study was approved by the Ethics Committee of the Pasteur University Hospital (Nice, France). Enrolment of patients took place after written informed consent had been obtained by parents, legal guardian and children when possible. Inclusion criteria were as follows: children (younger than 18 years) treated for solid tumour disease and chemotherapy protocol including at least three courses of vincristine. Patients were treated according to the protocol in use for their underlying malignancy. Concomitant antiemetic drugs prescribed as preventive treatment were ondansetron, alizapride and methylprednisolone 1 mg/kg/day. Administration of other cytotoxic drugs and the use of hyperhydration depended on the specific protocol.

Study design

The cohort was composed only of Caucasian-origin patients, and patient characteristics are summarized in Table 1. Children were followed up over three courses of vincristine which were not always at the same stage of the protocol. In this study, 1.5 mg/m² of vincristine was administered as an i.v. bolus injection (VINCRISITNE TEVA®, 1 mg/ml sulphate solution), and the interval between courses was at least 1 week. All drug infusions were followed by rinsing two times the catheter with 25 ml of saline, and blood samples were drawn from the central venous catheter. A maximum dose of 2 mg per cure was tolerated. The vincristine dose could be modified between the different courses in case of vincristine-induced neurotoxicity. Nine blood samples per patient were drawn over the 3 courses, following a sparse sample strategy with 3 different schedules: 10, 60 and 1,440 min; 30, 90 and 720 min; 10, 30 and 240 min after vincristine administration. The 3 schedules of administration were randomized for each child. Heparinized blood samples (5 ml) were centrifuged within 3 h of sampling at 4°C, at 1,000*g* for 10 min and stored at −80°C until analysis. One additional sample was drawn at the first course for genotype determination.

Determination of vincristine concentration

Vincristine plasma concentrations were measured by a validated LC–MS/MS method in the Laboratory of Pharmacokinetics and Toxicology of the Timone University Hospital [17]. The limit of quantification of the assay was 0.25 ng/ml, and the calibration curve was linear up to 50 ng/ml. Intra-day precision and accuracy ranged from 6.3 to 10% and from 91.9 to 100.8%, respectively. Inter-assay precision and accuracy ranged from 3.8 to 9.7% and from 93.5 to 100.5%, respectively.

Table 1 Patient's characteristics

	Patients (%)
Age (years)	
2–5	4 (15)
6–9	11 (42)
10–16	11 (42)
Sex	
M	15 (58)
W	11 (42)
Weight (kg)	
10–20	11 (42)
20–40	9 (35)
40–75	6 (23)
Body surface area (m^2)	
0.5–0.7	7 (27)
0.7–1.0	10 (38)
1.0–1.8	9 (35)
Tumour diseases	
Ewing's sarcoma	6
Burkitt's lymphoma	3
Pilolytic astrocytoma	2
Rhabdomyosarcoma	2
Wilms tumour	2
Medulloblastoma	2
Neuroblastoma	2
Low-grade glioma	2
Rhabdoid tumour of the kidney	1
Corticosurrenaloma	1
Myofibroblastic tumour	1
Settle's syndrome	1
Ependymoma	1
Treatment	
Monochemotherapy	5 (19)
Polychemotherapy	21 (81)
Administration of corticostreroids	14 (54)
Hyperhydration	14 (54)

Genotype determination

CYP3A4 and CYP3A5

The *CYP3A4*1B* (−392A > G in the promoter region) and *CYP3A5*3* polymorphisms (6,986 A > G in the intron 3) were analysed using real-time PCR assays and fluorescence resonance energy transfer with a LightCycler™ Instrument (Roche Diagnostic, Manheim, Germany). PCR Primers and specific probes were designed from published sequences (http://www.ncbi.nlm.nih.gov/) according to the gene GenBank sequences NM_017460 and NG_000004 for *CYP3A4* and *CYP3A5*, respectively. PCR analysis of *CYP3A5*3* allelic variant was applied to each DNA sample, as described previously [18]. PCR analysis for the determination of *CYP3A4*1B* was performed in a final volume of 20 µl, containing 200 ng of genomic DNA, 0.5 µM of each primer (MWG Biotech, Roissy, France), 0.2 µM of deoxyribonucleoside triphosphate, 1× PCR buffer, 2 mM $MgCl_2$ and 0.16 U of eurobiotaq DNA polymerase (Eurobio, Courtaboeuf, France). Specificity and size of different PCR fragments were verified in ethidium bromide-stained agarose gels. After initial denaturation for 2 min at 94°C, amplicons were generated for 40 cycles of 45 s at 94°C, annealing 45 s at 55°C and 45 s at 72°C, followed by a 7-min final extension step at 72°C. For *CYP3A4*1B* and *CYP3A5**3 allelic variants, fluorescence detection was performed with 0.2 µM of each hybridization probe (Sigma-Proligo, Paris, France). Melt curve analysis followed the amplification stage with a temperature increase from 52 or 45°C to 80°C at a ramp rate of 0.2°C/s, respectively. Melting peaks for the *CYP3A4* alleles were at approximately 59°C for the mutated allele (**1B*) and 62°C for the wild-type allele (**1A*). Melting peaks for the *CYP3A5* alleles were at approximately 55°C for the mutated allele (**3*) and 61°C for the wild-type allele (**1*).

ABCB1

ABCB1 polymorphisms (C1236T in exon 12, G2677T(A) in exon 21, and C3435T in exon 26) were also analysed using real-time PCR assays. The PCR primers and hybridization probes were synthesized by Proligo (Paris, France). PCRs were performed in a final volume of 20 µl, containing 200 ng of genomic DNA, 0.5 µM of each primer, 0.2 µM of deoxyribonucleoside triphosphate, 1× PCR buffer, 2 mM $MgCl_2$ and 0.16 U of eurobiotaq DNA polymerase (Eurobio, Courtaboeuf, France). Specificity and size of different PCR fragments were verified in ethidium bromide-stained agarose gels. After initial denaturation for 2 min at 94°C, amplicons were generated for 35, 45 and 40 cycles of 30 s at 94°C for exon 12, 21 and 26, respectively, annealing 30 s at 60, 58 and 55°C, respectively, and 30 s at 72°C, followed by a 7-min final extension step at 72°C. Melt curve analysis followed the amplification stage with a temperature increase from 48 or 50°C to 95°C at a ramp rate of 0.2°C/s. Melting peaks were approximately 65, 53, 65°C for mutated alleles and 60, 56, 58°C for wild-type alleles, for C1236T, G2677T and C3435T polymorphisms, respectively.

Estimation of haplotype frequencies for *ABCB1* was performed using the Phase 2.1 program (http://www.stat.washington.edu/stephens/software.html), based on a standard expectation–maximization algorithm to reconstruct individual haplotypes from population genotype data [19].

Population pharmacokinetic analysis

Population PK analysis of vincristine was performed using a non-linear mixed-effects model as implemented in the NONMEM computer program (version 6.2) [20]. Population predictions (PRED) from the NONMEM analysis subroutines ADVAN 3, TRANS 4 were employed for the 2-compartment model. Intersubject variability (ISV) as well as interoccasion variability (IOV) were evaluated. Several error models (additive, proportional, or both) were investigated to describe residual variability. Performance of the model was judged by both statistical and graphic methods [21, 22]. The minimal value of the objective function as calculated by NONMEM was also used to assess the goodness of fit. An increase in goodness of fit was accompanied by a decrease in objective function, and this decrease was asymptotically distributed as a χ^2 distribution. Furthermore, SEs were calculated by the use of the COVARIANCE option of NONMEM. For graphic model diagnostic, the following graphs were compared: observed concentrations (DV) versus prediction (PRED), weighted residuals (WRES) versus time, weighted residuals versus PRED and individual predictions (IPRED) versus DV.

A first analysis was performed to find the base model that best described the data. Once it was defined, the influence of each covariate on PK parameters was tested. These covariates were age, sex, body surface area, administration of corticosteroids, hyperhydration, polychemotherapy or monochemotherapy, *CYP3A4* and *CYP3A5* polymorphisms and *ABCB1* haplotypes. The diagnostic plots described above, the change in objective function and the change in parameter variability were noted in order to select those improving the model prediction. A decrease in the objective function value of at least 6.61 (χ^2 distribution with 1 degree of freedom for $P < 0.01$) relative to the base PK model was required for the addition of a single parameter in the model. Bootstrap procedures were performed using Wings for NONMEM (http://www.wfn.sourceforge.net) to evaluate the 95% confidence interval (CIs) non-parametrically. A total of 637 bootstrapped data sets were generated by resampling subjects from the original data set with replacement. These data sets were analysed using the final model described previously. Finally, the 2.5th and the 97.5th percentiles of the parameters estimated were taken to build the 95% bootstrap percentile CIs. In order to performe a visual predictive check, the final model and the corresponding parameters values (including interindividual variability and residual variability) were used to simulate 637 replicates using the SIMULATION, SUBPROBLEM feature in NONMEM (Monte Carlo simulation).

Individual pharmacokinetic parameters were determined for each course by Bayesian estimation using the final model.

Table 2 Genotype frequencies of *CYP3A4*, *CYP3A5* and *ABCB1* in 24 paediatric patients receiving vincristine

Single-nucleotide polymorphism	wt/wt	wt/m[a]	m/m
*CYP3A4*1B* (−372A > G)	21 (87.5)	3 (12.5)	0
*CYP3A5*3* (6986A > G)	0	5 (20.8)	19 (79.2)
ABCB1 exon 12 (C1236T)	13 (54.2)	6 (25.0)	5 (20.8)
ABCB1 exon 21 (G2677T)	13 (54.2)	7 (29.2)	4 (16.6)
ABCB1 exon 26 (C3435T)	7 (29.2)	13 (54.2)	4 (16.6)

Values are presented as *n* (%)

[a] *wt* wild type, *m* mutated

Results

Patients and treatment

A total of 26 children were included in the study during the follow-up period. Of 26 patients participating at the study, pharmacokinetic analysis could not be performed in one and genotyping in two because blood sampling was not possible. Five patients did not complete the three cures owing to neurotoxicity, resulting in 67 cures available for pharmacokinetic analysis. A mean dose of 1.33 ± 0.28 mg/m² of vincristine was administered.

Frequencies of CYP3A4, CYP3A5 and ABCB1 SNPs

Table 2 shows the frequency distributions of *CYP3A4*, *CYP3A5* and *ABCB1* genotypes in 24 paediatric patients treated with vincristine. No genotype deviated from Hardy–Weinberg equilibrium and SNP frequencies were consistent with previous studies in a Caucasian population [13, 23]. Concerning the *CYP3A4*1B* allelic variant, none of the patients was carrying the *CYP3A4*1B/*1B* genotype, confirming its very low frequency in Caucasians. In contrast, for the *CYP3A5*3* allelic variant, the homozygous genotype *CYP3A5*3/*3* was observed in 19 patients (79.2%), the heterozygous genotype *CYP3A5*1/*3* in 5 patients (20.8%) while the wild-type genotype *CYP3A5*1/*1* was not observed in our population.

ABCB1 haplotypes were estimated from the three *ABCB1* genotypes (C1236T, G2677T, C3435T) using a standard expectation–maximization algorithm. The three major haplotypes observed were CGC, TTT and CGT, accounting for 50.0, 23.2 and 14.6% of the total diversity, respectively. The combination of these three *ABCB1* genotypes constituted the three major diplotypes observed in

Table 3 Population PK parameters of vincristine

Parameter	Estimation		Bootsrap		
	Final estimation	SE (%)	Median	95% CI*	
PK					
CL (L/h/m^2)	12.6	13.3	12.1	9.08	15.4
V1 (L/m^2)	15.7	14.0	15.9	10.4	23.0
Q (L/h/m^2)	51.1	13.9	51.9	36.2	90.2
V2 (L/m^2)	146	8.9	145	105	202
ISV ω (%)					
ω (CL)	36.3	99.2	34.9	0.338	63.4
ω (Q)	60.1	39.2	63.5	37.0	92.3
IOV CL (%)	76.0	34.3	80.4	44.1	112
Residual variability					
σ proportional (%)	51.6	32.1	53.0	38.8	66.4

CL clearance, *V1* first compartment volume of distribution, *Q* intercompartmental clearance, *V2* second compartment volume of distribution, *ISV* intersubject variability, *IOV* interoccasion variability, *SE* standard error, expressed as percentage, *CI* confidence interval

* The 2.5th and 97.5th percentiles of 637 bootstrap distribution of parameter estimates

this study, CGC-CGC (25.0%, $n = 6$), CGC-CGT (20.8%, $n = 5$) and CGC-TTT (20.8%, $n = 5$).

Population pharmacokinetic analysis

Data from 184 samples were collected from the patient population. Vincristine plasma concentrations ranged from 0.40 to 89.6 ng/ml. The 2-compartment model provided a good description and thus was kept as the base model. The ISV on clearance (CL), intercompartmental clearance (Q) and residual variability were modelled as proportional. The ISV could not be estimated for the first (V1) and the second (V2) compartment volume of distribution. The IOV could only be estimated for the CL. The final PK estimate parameters are summarized in Table 3. Population terminal half-life ($t_{1/2\beta}$) was 11.8 h and the area under curve was 135 h mg/l. Table 3 shows the values of medians and 95% CIs obtained from bootstrap procedures. Figure 1 describes the observed vincristine concentrations versus time with the median prediction and the 95% prediction CI obtained from the simulation. No formal bias was observed in the goodness-of-fit plots (data not shown). We observed great variability in individual vincristine CL, as shown in Fig. 2.

None of the demographic (age, sex, body surface area) or therapeutic (administration of corticosteroids, hyperhydration, polychemotherapy or monochemotherapy) covariates assessed was associated with a decrease in the objective function, and therefore, none was retained in the two final models. *CYP3A4*, *CYP3A5* genotypes and *ABCB1* haplotypes did not improve the model prediction as well. Figure 3 represents the individual Bayesian estimation of the CL according to the different *CYP3A4* and *CYP3A5* genotypes.

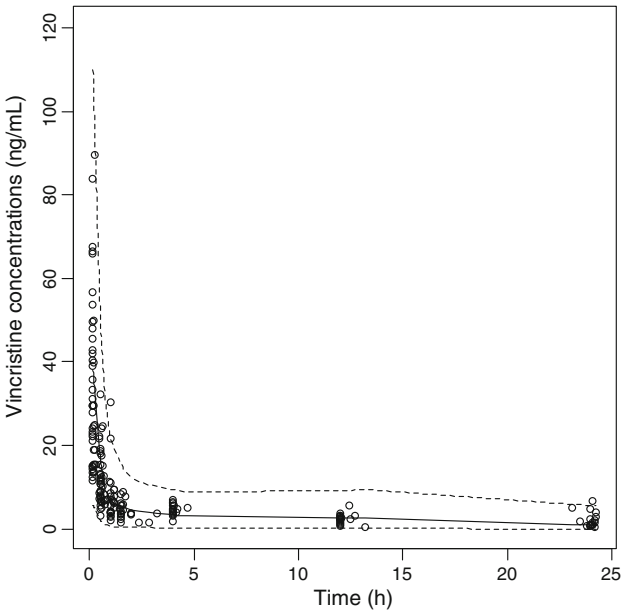

Fig. 1 Observed (*ring*) and simulated (*solid line* median and *dotted lines* 95% population predicted interval) vincristine concentrations versus time in patient population

Discussion

The present study provides a population pharmacokinetic analysis of vincristine in a paediatric population with solid tumour diseases. To our knowledge, this is the only pharmacokinetic population study, using for vincristine quantification, a highly specific and sensitive method via tandem mass spectrometry detection. This analytical method makes it possible to separate the parent drug from its metabolites

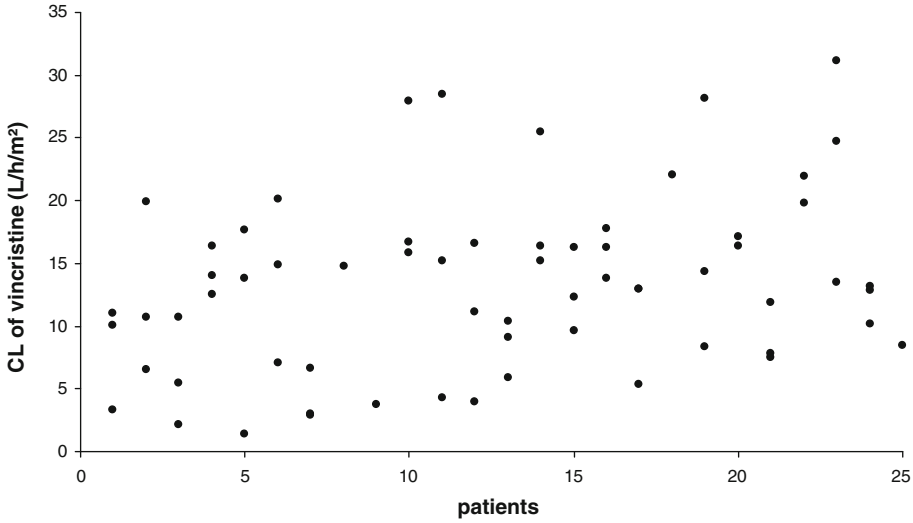

Fig. 2 Distribution of vincristine individual Bayesian estimation of the clearance

and provides more accurate information about pharmacokinetics, as recommended in a recent review [24]. The population pharmacokinetics of vincristine was well fitted by a two-compartment model, and pharmacokinetic parameters (CL and Q) showed considerable interindividual variability.

Previously, vincristine pharmacokinetics has been successfully described by a three compartment open model [25]. However, in our study, both models were tested and vincristine pharmacokinetics was best fitted by a two-compartment model, as also recently reported in two recent studies [2, 3].

Comparison with previous studies is difficult owing to the differences in the population. A few data are available on vincristine pharmacokinetics in children, particularly in solid tumour diseases. Compared with the only study in paediatric patients with solid tumour disease, we observed a comparable Cl but a higher V2 [26]. However, the administration schedule was different since a 1.5 mg/m² vincristine bolus administration followed by 96-hour continuous infusion was administered instead of a single bolus in our study.

In previously described studies in paediatric patients with leukaemia, higher CL (25.7 and 13.4 l/h/m²) were reported compared with our results [7, 8]. This difference can be explained by the concomitant administration of high-dose steroids in the therapeutic protocol of ALL, although they were used at lower dose in our study, as antiemetic. Indeed, an increase in vincristine CL has been demonstrated in patients receiving concomitant high-dose steroids as part of multi-agent chemotherapy [8, 27]. This drug–drug interaction is explained by the induction of CYP3A4 by corticosteroids. In our population, low-dose steroids were administrated and no influence on pharmacokinetic parameters was observed. Finally, our population pharmacokinetic parameters are equivalent to those reported in studies using low-dose or no steroid [1, 27].

Vincristine pharmacokinetics is characterized by great interindividual variability also observed in our population [1, 28]. To understand the origins of this variability, different factors have been studied (age, sex, body surface area, dosage per m², biochemical variables and tumour diseases), but discordant results have been reported and none of these factors explained this variability [1, 7, 29]. We showed comparable results with no apparent effect of age, sex, body surface area and hyperhydration on vincristine pharmacokinetic parameters. Modifications of drug pharmacokinetics by hyperhydration have been described for hydrophilic drugs with a limited volume of distribution (*Vd*) [30]. Vincristine is a lipophilic drug with major *Vd* and therefore influence of hyperhydration on pharmacokinetic parameters is not expected.

The hypothesis has been raised that *CYP3A4* and *CYP3A5* genes could influence vincristine pharmacokinetics, therapeutic response and toxicity [10–12]. The *ABCB1* gene, encoding the efflux pump P-gp, affects the distribution of drugs such as vincristine. Therefore, we selected and genotyped several polymorphisms of interest of *CYP3A4*, *CYP3A5* and *ABCB1*. No impact was observed on vincristine pharmacokinetic parameters in our population, and the major interindividual variability observed in vincristine pharmacokinetics cannot be explained by these genetic factors. In 2004, Plasschaert et al. [31] have previously studied the impact of the *ABCB1* SNPS C3435T and G2677T on vincristine pharmacokinetics and no association was observed. A linkage disequilibrium has been described between the G2677T SNP and both C3435T and C1236T SNPs, suggesting that assessing the impact of ABCB1 haplotypes instead of the individual genotypes may be of greatest interest. However, we did not find either a relationship between ABCB1 haplotypes and pharmacokinetics of vincristine. Consequently, *ABCB1* polymorphisms are not expected to impact vincristine-induced neurotoxicity.

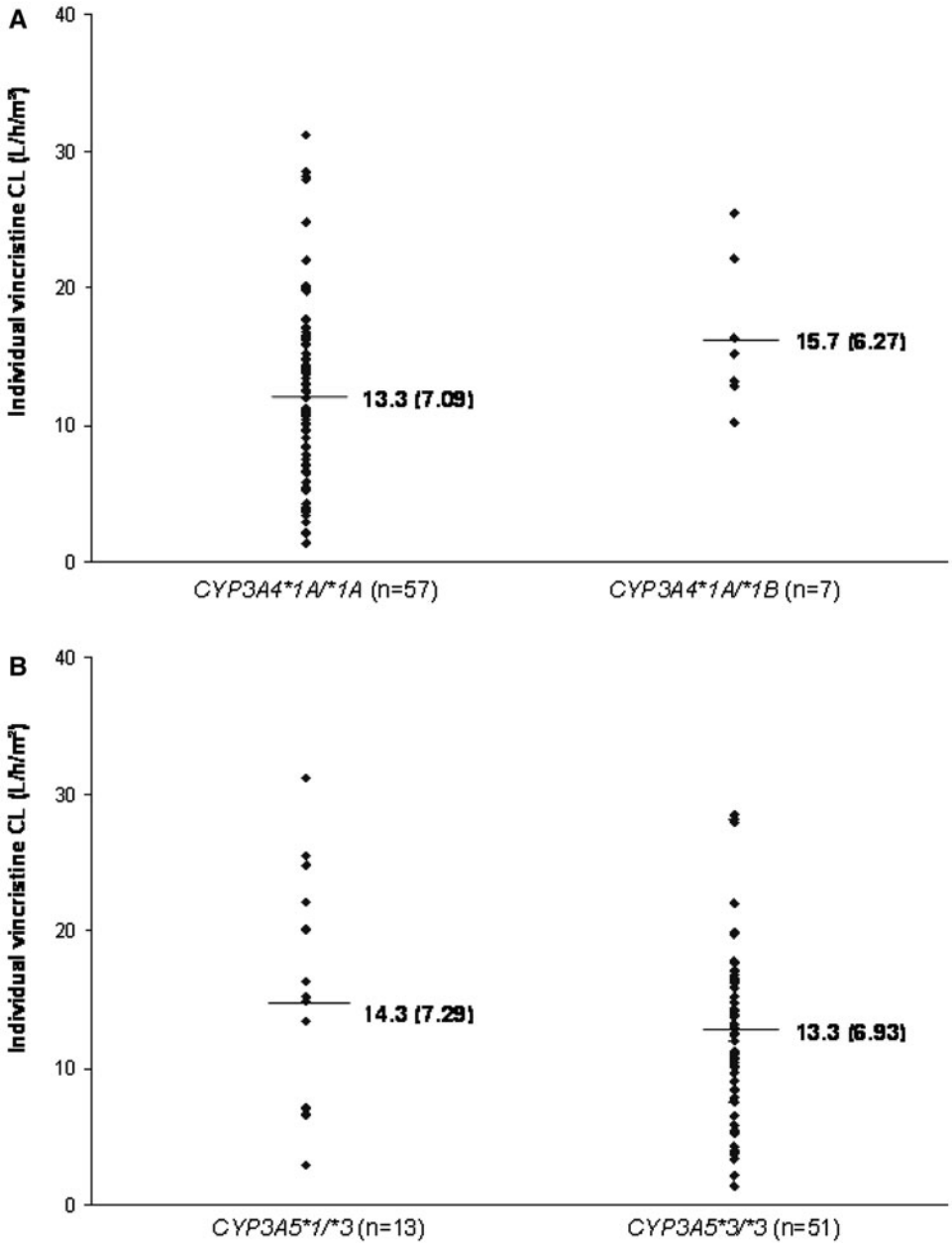

Fig. 3 Vincristine individual Bayesian estimation of the clearance according to CYP3A4 and CYP3A5 genotypes. *Horizontal bars* depict median values (Inter Quartile Range)

A recent study which reported no influence of *CYP3A5* or *ABCB1* polymorphism on impaired motor performance in children with ALL confirms this hypothesis [32].

However, these results are discordant with data observed both in vitro and in other clinical studies based on phenotypic observations. The lack of relationship between pharmacokinetics and genetics may be due to a limited number of patients and a low allele frequency of some studied polymorphisms, though our population was of a good size for a paediatric study.

To our knowledge, the present work is the first clinical study assessing the impact of different *CYP3A4*, *CYP3A5* and *ABCB1* SNPs on vincristine pharmacokinetics in paediatric patients treated for solid tumour diseases. Our results suggest that vincristine pharmacokinetic variability cannot be strictly explained by genetic polymorphisms, but they may contribute in association with other factors. This hypothesis is enhanced by the observation of a great IOV on CL, also observed on the individual Bayesian estimation of the CL (Fig. 2).

Perhaps, an impact of genetic polymorphisms on vincristine pharmacokinetics could be observed in a larger patient cohort or by performing a pharmacogenetics approach that could unveil important genes not suspected to be involved in vincristine metabolism.

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