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ORIGINAL ARTICLE

Developmental pharmacokinetics of etoposide in 67 children: lack of dexamethasone effect

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Abstract
Purpose A randomized clinical trial examined whether dexamethasone administration prior to ondansetron followed by etoposide and carboplatin infusions, and single-nucleotide polymorphisms (SNPs) of *CYP3A4*, *CYP3A5* and *MDR1* genes could modify etoposide pharmacokinetics in pediatric patients.
Methods Patients, 67 children, aged 14 weeks to 16.7 years, were treated for various malignancies and received either 3- or 5-day courses of etoposide and carboplatin: these two drugs were always administered after ondansetron infusion but combined or not with dexamethasone 5 mg/m^2/day 30 min prior to etoposide infusion. Population pharmacokinetics was modeled using a non-linear mixed effect model program (Monolix version 31 s).
Results Etoposide pharmacokinetics was ascribed to a 2-compartment model. The most significant covariate effect was bodyweight (BW), so the parameters were standardized to a 70-kg BW using the allometric ¾ or 1 power model for clearance (CL, Q) or volume terms (V), respectively. The population means for clearance and central volume of distribution were 2.05 l/h/70 kg and 9.21 l/70 kg with the corresponding between-subject variabilities, 0.26 and 0.28. Dexamethasone treatment had no effect on CL, either at the first or at the last administration occasion. CYP3A and MDR1 examined SNPs had no significant effect.
Conclusion Pharmacokinetics of etoposide was influenced by BW on an allometric basis in this pediatric population. Dexamethasone did not influence etoposide

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pharmacokinetics during these 3–5 days courses. These results should allow a better individualization of etoposide dosing in children.

Keywords Etoposide · Dexamethasone · Population pharmacokinetics · Children · Anticancer drugs · Genetic polymorphisms

Introduction

Chemotherapy combining etoposide and carboplatin has been proven effective in the treatment of children with various cancer diseases, including medulloblastoma [1], neuroblastoma [2], nephroblastoma [3] and retinoblastoma [4]. This highly potent chemotherapy is often associated with nausea and vomiting in children during and after the treatment period. The prevention of these adverse effects in children usually includes a combination of dexamethasone and ondansetron [5]. However, as etoposide is O-demethylated by cytochromes P450 (CYP) CYP3A4 and CYP3A5, dexamethasone could influence etoposide elimination via some effects on these CYPs [6]. Moreover, single-nucleotide polymorphisms (SNPs) in *CYP3A4* and *CYP3A5* genes may modify enzymatic activity and then influence etoposide drug elimination rate. Indeed, a decrease in CYP3A4 activity has been associated with an SNP in the 5′-regulatory region of the *CYP3A4* gene (−392A > G), named CYP3A*1B. Besides, the frequent SNP in intron 3 of the *CYP3A5* gene (CYP3A5*3) results in an inactive truncated protein [7, 8]. Furthermore, as etoposide is a substrate of the P-glycoprotein, encoded by the *MDR1* gene, *MDR1* gene SNPs could also modify etoposide disposition [9].

The objectives of this study were then to develop a population pharmacokinetic model for etoposide in pediatric patients and to examine a possible dexamethasone effect on etoposide elimination, including the research of other covariates as well as the effects of the SNPs of *CYP3A4*, *CYP3A5* and *MDR1* genes on etoposide clearance.

Methods

This randomized open clinical trial examined whether dexamethasone could modify etoposide pharmacokinetics in pediatric patients. All children had a documented cancer and were randomly allocated to either the single ondansetron or the combined ondansetron–dexamethasone antiemetic therapy group. This study was approved by the regional ethics committee, and written consent was obtained from the parents before inclusion. Appropriate information had to be given to patients according to their age, and assent of the oldest children and adolescents was necessary before study initiation. Patients aged 3 months to 16 years with a bodyweight greater than 4.5 kg and receiving the etoposide/carboplatin chemotherapy were eligible.

Patients received a 1-h etoposide infusion followed by a 1-h carboplatin infusion on 3 or 5 successive days (3-day chemotherapy: etoposide 150 mg/m^2/day etoposide and 200 mg/kg/day carboplatin, except for children <1 year old or <10 kg, 5 mg/kg/day etoposide and 6.7 mg/kg/day carboplatin; 5-day chemotherapy: etoposide 100 mg/m^2/day etoposide and 160 mg/m^2/day carboplatin, except for children <1 year old or <10 kg, 3.3 mg/kg/day etoposide and 5.3 mg/kg/day carboplatin). Thirty minutes prior to chemotherapy, patients received ondansetron 5 mg/m^2/day combined or not to dexamethasone 5 mg/m^2/day.

For most patients, two pharmacokinetic evaluations took place on the first and last day of chemotherapy. Four sampling times per evaluation were randomly drawn from the following set: 5, 15, 30 min, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 h following the end of infusion. Blood samples were immediately centrifuged to yield plasma. Etoposide was essayed in 100 µl plasma samples by high-performance liquid chromatography with teniposide as internal standard and fluorometric detection according to a validated method [10]. The limit of quantification was 0.1 mg/l.

DNA extraction and genotyping

Blood samples were collected for genotyping after obtaining a written informed consent from parents. Genomic DNA was extracted from peripheral blood leukocytes using the Blood Mini Kit DNA (Qiagen, Courtaboeuf, France) according to standard protocols and stored at −80°C until use. For the SNPs 6986A > G of *CYP3A5* gene (CYP3A5*3; rs776746), 2677G > T/A (exon 21; rs2032582) and 3435C > T (exon 26; rs1045642) of *MDR1* gene, alleles were determined by using Taq Man® Assay Reagents and probes for allelic discrimination (TaqMan® SNP Genotyping Assays, Applied Biosystems, Courtaboeuf, France) with a 7900HT Applied Biosystems thermal cycler. For the SNP −392A > G of CYP3A4 (CYP3A4*1B; rs2740574), primers and probe set were designed using the custom TaqMan® SNP Genotyping Assays Service (Applied Biosystems). Sequences are available upon request.

Population pharmacokinetic modeling

Data were analyzed using the nonlinear mixed effect modeling software program Monolix version 31s [11] (http://www.wfn.software.monolix.org). Parameters were estimated by computing the maximum likelihood estimator

of the parameters without any approximation of the model (no linearization) using the stochastic approximation expectation maximization (SAEM) algorithm combined with an MCMC (Markov Chain monte Carlo) procedure. The number of MCMC chains was fixed to five for all estimations. A proportional model was used to describe the residual variability, and the between-subject variabilities (BSV) were ascribed to an exponential model. Parameter shrinkage was calculated as {1-sd(eta)/omega}, where sd(eta) and omega are the standard deviation of individual eta parameters and the population model estimate of the BSV, respectively. For the SNPs of *CYP3A4, CYP3A5* and *MDR1* genes, all the genotypes effects (nine parameters) were estimated together relative to the wild type (baseline CL). Then, at each successive step the genotype effect with the less significant parameter (with the greatest p value) was removed. Moreover, the Likelihood Ratio Test (LRT), including the log-likelihood, the Akaike information criterion (AIC) and the bayesian information criterion (BIC), was used to test different hypotheses regarding the final model, covariate effect on pharmacokinetic parameter(s), residual variability model (proportional versus proportional plus additive error model), and structure of the variance–covariance matrix for the BSV parameters. Diagnostic graphics and other statistics were obtained using the R program [12].

Results

From the 67 patients investigated, 566 time-plasma concentrations were available for analysis. Nine concentrations were reported below the limit of quantification (BLQ) and considered as left-censored data in the modeling process. Patient characteristics are summarized in Table 1.

A two-compartment open model adequately described etoposide data. BSV was estimated for all structural parameters with a covariance term between the clearance (CL) and central volume of distribution (Vc). Residual variability was described by a proportional error model. At this step, CL was 0.69 l/h (relative standard error, rse 7%) per a mean 20.6 kg BW, and the corresponding BSV was 53% (rse 2%).

Table 1 Characteristics of the 67 pediatric patients

Item	n	Mean	Median	Range
Age (year)	67	5.35	3.52	0.27–16.7
Bodyweight (kg)		20.6	15	5.3–66
Height (cm)		105	100	60–172
Serum creatinine (μM)		48	79	15–650
Total bilirubin (μM)		6.7	6.0	2–17
Tumor type				
Medulloblastoma	18			
Neuroblastoma	26			
Nephroblastoma	7			
Retinoblastoma	5			
Miscellaneous	11			

The main covariates effects on all pharmacokinetic parameters were BW and age (Fig. 1), so the pharmacokinetic parameters were allometrically normalized for BW to a 70-kg individual as follows,

$$\mathrm{Pi} = \mathrm{P_{TYPICAL}} \times (\mathrm{BWi}/70)^{\mathrm{PWR}},$$

where i denotes the ith individual. The PWR exponents were ¾ and 1 for the clearance and volume terms, respectively. This significantly decreased all BSV estimates (BSV of CL decreased from 53 to 28%) and improved the predictive performance of the model (observed concentrations vs. model predicted concentrations). Thereafter, an additional age effect was investigated using a sigmoid Emax model relating the post-menstrual age (PMA = post-natal age + 40 weeks) to a fractional value for mature clearance, $F_{PMA} = PMA^h/(PMA50^h + PMA^h)$, where PMA_{50} is the PMA at which $F_{PMA} = 0.5$ and h is the Hill coefficient. This did not improve the model, and the PMA_{50} and h estimates were not significant with much more than 50% relative standard errors. The effect of age was finally removed by the BW allometric scaling.

The dexamethasone effect on etoposide CL was allowed to be different on the first and second occasion (3–5 days later). Without dexamethasone (control treatment), etoposide CL estimates on the 1st and 2nd occasions were not significantly different. Thereafter, there was no significant difference between etoposide CL estimates without or with a previous infusion of dexamethasone, on the 1st or 2nd occasion, the CL variations relative to the control were lower than 2%.

Table 2 shows the distribution of *CYP3A4*, *CYP3A5* and *MDR1* genotypes in the 67 children. No significant effects of *CYP3A4, CYP3A5* or *MDR1* gene SNPs on etoposide pharmacokinetics were observed. There was a trend in CL increase, +9%, in patients with the CYP3A5*1*3 genotype (Wald test, $P = 0.09$, $n = 10$ patients in this group).

Table 3 summarizes the final population pharmacokinetic estimates. Most of the parameters were well estimated with low relative standard errors. The empirical Bayesian estimate shrinkages were generally low, only the peripheral pharmacokinetic parameters, Q and Vp had shrinkage estimates between 20 and 25%.

The results of the visual predictive check (VPC) are depicted in Fig. 2. The patients received generally a dose normalized by size. Therefore, the VPCs were finally stratified according to the first and last infusion,

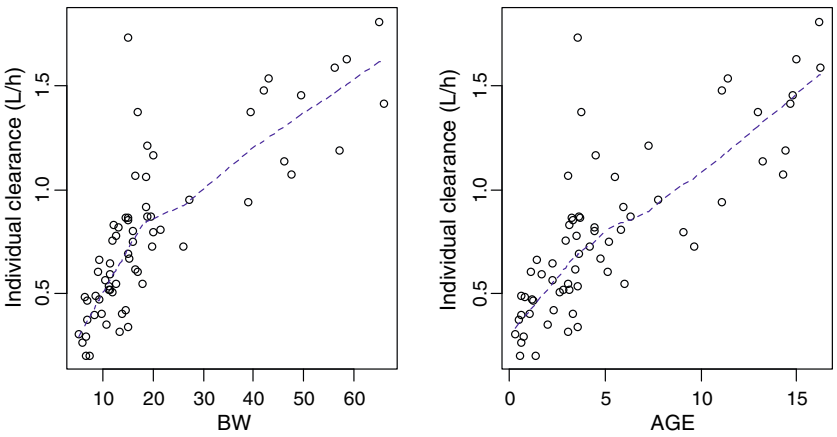

Fig. 1 Relationships between the empirical Bayes estimates (EBE) of etoposide clearance, in L/h, from the basic model and bodyweight (BW in kg) and age (years) in 67 pediatric patients. The *dashed lines* are drawn after a spline function. The median of EBE clearance estimates is 0.74 l/h (range 0.21–1.84)

Table 2 Genotypes of CYP3A4, CYP3A5 and MDR1 in 67 pediatric patients

	CYP3A5*3*3	CYP3A5*1*3	CYP3A5*1*1
CYP3A4 *1A*1A	55	6	0
CYP3A4 *1A*1B	1	3	0
CYP3A4 *1B*1B	0	1	1
	MDR1 3435 CC	MDR1 3435 CT	MDR1 3435 TT
MDR1 2677 GG	16	5	2
MDR1 2677 GA	1	0	0
MDR1 2677 GT	1	26	7
MDR1 2677 TT	0	2	7

respectively. For all groups, the observed concentrations were centered about the model-predicted median, and the proportion of observations out of the model-predicted 5th and 95th percentile curves were not significantly different from 10%.

Based on individual etoposide clearance estimates and drug dosages, the mean total etoposide exposure (area under the curve or AUC) was 371 (±94) or 474 (±127) mg h/l for the 3- or 5-day chemotherapy, respectively (significant difference, Kruskal–Wallis rank sum test $P = 0.0003$). Given the significant relationship between clearance and bodyweight, the etoposide dosage targeting these drug exposures, 371 and 474 mg h/l, were compared to the actual drug exposure. Figure 3 shows the great variability achieved in etoposide exposure with the actual dosage, particularly for the smallest, youngest, patients and the difference between the actual drug dosage and a candidate drug dosage aimed to target the same AUC for each therapeutic modality (Dose $= 2.05.(\text{BW}/70)^{3/4}$ $\text{AUC}_{\text{target}}$).

Discussion

The pharmacokinetics of plasma etoposide in pediatric patients was satisfactorily described by an open two-compartmental model with linear elimination. The administration of dexamethasone in addition to ondansetron as antiemetic therapy, prior to etoposide-carboplatin infusions, had no significant effect on etoposide CL. The etoposide CL estimate, 2.05 l/h/70 kg was close to previously reported estimates in adult patients, 1.8 l/h [13] or 2.65 l/h [14], supporting the BW allometric scaling of pharmacokinetic parameters. Moreover, in a population of 18 infants aged 2.5–14 months (median 10 months), the estimated CL was 6.3 ml/min/8 kg

Table 3 Parameter estimates of the final etoposide population model in 67 pediatric patients (14 weeks–16.7 years)

Parameter	Covariate effect	Estimate (%rse)	BSV (% rse) [shrinkage]
CL_{70} (l/h/70 kg)	$CL = CL_{70}\ (BWi/70)^{3/4}$	2.05 (4)	0.27 (9) [0.04]
Vc_{70} (l/70 kg)	$Vc = CL_{70}\ (BWi/70)^{1}$	9.3 (5)	0.28 (15) [0.19]
Q_{70} (l/h/70 kg)	$Q = CL_{70}\ (BWi/70)^{3/4}$	0.68 (15)	0.96 (10) [0.21]
Vp_{70} (l/70 kg)	$Vp = CL_{70}\ (BWi/70)^{1}$	5.7 (8)	0.53 (13) [0.23]
Residual variability	NA	Proportional	0.222 (4) [0.12]

Parameters are normalized after a 70-kg patient according to allometric scaling

% rse percent relative standard error; *BSV* between-subject variability; *CL* and *Q* elimination and intercompartmental clearances; *Vc* and *Vp* central and peripheral volumes of distribution; the *subscript "70"* indicates the parameter estimates are normalized to a 70-kg bodyweight; BWi, individual bodyweight. The correlation between CL and Vc BSVs is 0.89. Accordingly, the expected CL for a patient weighing 15 kg is $2.05 \times (15/70)^{3/4} = 0.75$ l/h

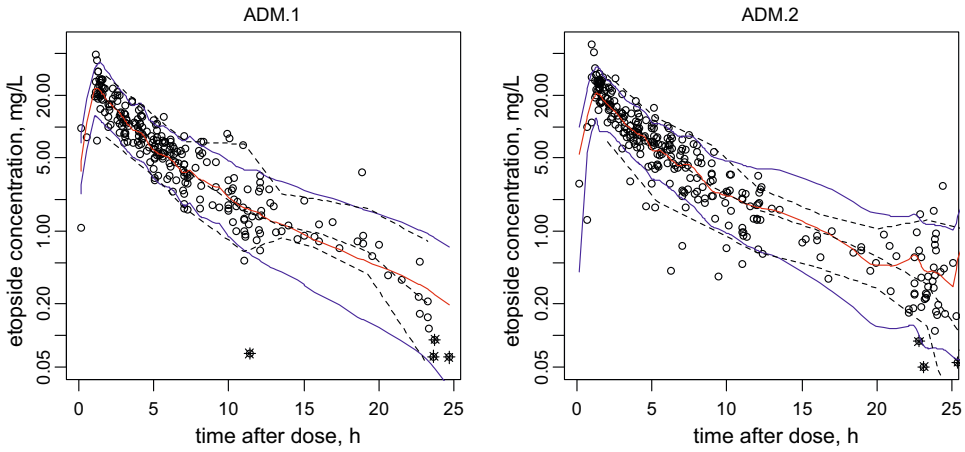

Fig. 2 Visual predictive check for the final etoposide population model in 67 children (14 weeks–17 years). *Panels ADM.1* and *ADM.2* denote the first etoposide or the second etoposide administration. The *solid lines* stand for the median, 5th and 95th percentiles of the simulated concentrations from the final model. The *dashed lines* stand for the median, 5th and 95th percentiles of the observed concentrations. *Asterisk* denotes the concentrations reported below the limit of quantification

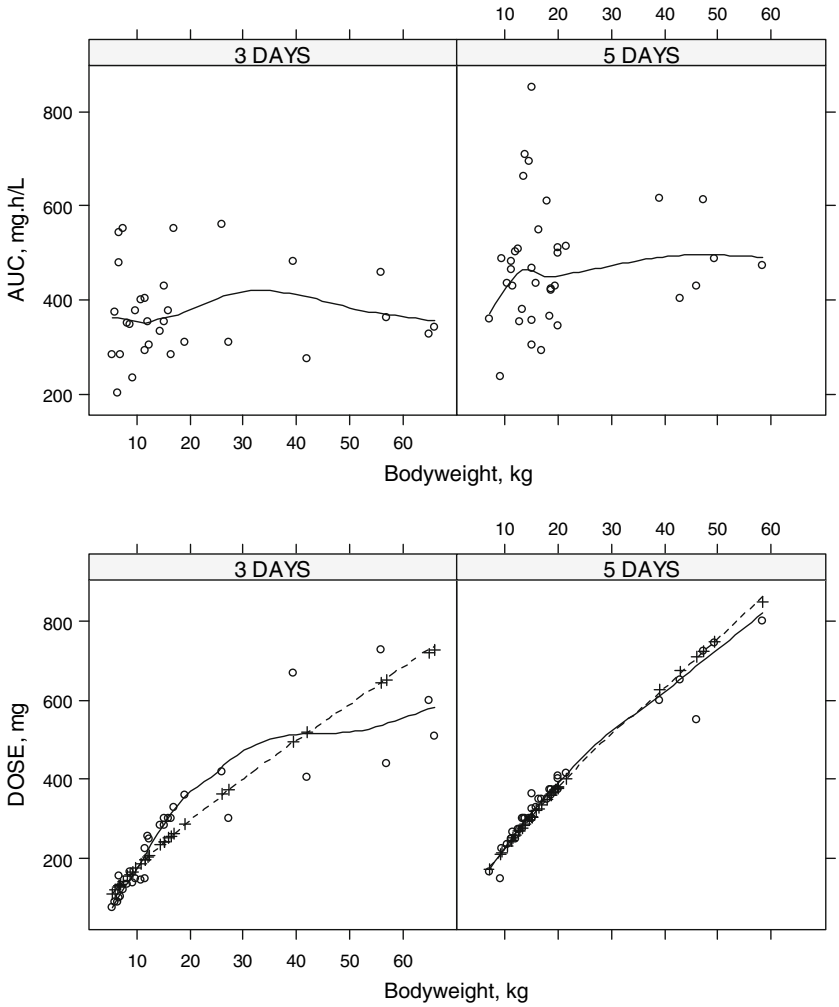

Fig. 3 Etoposide exposure (AUC) achieved on a 3 or 5-day chemotherapy (TOP) and etoposide total dose on a 3 or 5-day chemotherapy: (*open circle*, *solid line*) actual dose received or (*plus*, *dashed line*) dose based on a target AUC (BOTTOM), versus patient bodyweight (*BW*). Etoposide exposure is determined as AUC = (total dose)/(individual clearance), and the dose based on a target AUC is determined as $D = 2.05.(\mathrm{BW}/70)^{3/4}$ AUC (371 and 474 mg h/l for the 3 or 5-day chemotherapy). The *lines* are drawn after a spline function

or 0.38 l/h/8 kg [15], which according to the BW allometric scaling will be $0.38 \times (70/8)^{3/4} = 1.92$ l/h/70 kg. Also, in 45 pediatric patients aged 0.5–17.7 years, the estimated CL was 17.1 or 17.6 ml/min/m^2 according to two age groups, corresponding to 1.84 or 1.90 l/h/1.8 m^2 [16].

In developmental pharmacokinetic approaches, an effect of age on CL could generally be observed in addition to the BW allometric scaling [17]. This age effect explains a part of the CL maturation that is not dependent upon BW. However, in pediatric population, the age-related effect

independent of size effect cannot always be established. The reasons are generally a too small sample size or a lack of data in age group below 1 year, in which age group the age-related CL maturation is very fast. In our study, only eight patients were less than 1 year old, and only two were less than 6 months old.

No effect of prior dexamethasone administration on this short chemotherapy time period was observed. Kishi et al. [18] observed an increase in etoposide CL after a 29-day period of prednisone treatment, but could not definitively attribute this effect to an induction of CYP3As. Since several days of drug exposition are required to observe induction of CYPs and transporters (involving transcription and protein traduction), the 3–5 days exposition to dexamethasone in the present study appears to be too short to increase etoposide clearance.

Among other covariates, the CYP3A5*1*3 genotype was associated with a trend in CL increase (not significant). The CYP3A4 *1A*1B and *1B*1B genotypes included only 4 and 2 patients, respectively, and did not allow to show any significant CL changes in this population of 67 children. Finally, the lack of effect of *MDR1* gene SNPs are in accordance with the results of Tran et al. for docetaxel disposition [19]. Conversely, Kishi et al. showed that *MDR1* exon 26 CC genotype predicted higher day etoposide clearance. This discrepancy may be associated with a higher statistical power (greater number of patients) in their study [18].

Finally, there was a great variability in the achieved etoposide exposure, particularly in the youngest patients. This variability in exposure could be decreased if the drug dosage was aimed to target a particular exposure value, according to the patient clearance expected from bodyweight.

In conclusion, pharmacokinetics of etoposide was influenced by bodyweight on an allometric basis in this pediatric population. Dexamethasone did not influence etoposide pharmacokinetics. These results should allow a better individualization of etoposide dosing in children and the safe use of dexamethasone as an anti-emetic drug when etoposide is combined to carboplatin.

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