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Laurent Nguyen · Etienne Chatelut
Christine Chevreau · Brigitte Tranchand
Isabelle Lochon · Jean-Marc Bachaud · André Pujol
Georges Houin · Roland Bugat · Pierre Canal

Population pharmacokinetics of total and unbound etoposide

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Abstract A population pharmacokinetics study using the NONMEM program was undertaken to determine the effects of different covariates on the pharmacokinetic parameters of etoposide. A total of 1,044 plasma etoposide concentrations were determined by high-performance liquid chromatography (HPLC) in 100 patients (pts; 75 men and 25 women aged 25–85 years) treated for various tumor types with i.v. (57 pts) or oral (43 pts) etoposide. For 67 pts, etoposide plasma protein binding was determined by equilibrium dialysis; the unbound fraction ranged from 4% to 24%. A linear two-compartment model with first-order absorption (for oral dosing) accurately described the concentration versus time data. The central and peripheral volumes of distribution were significantly correlated with the body surface area [Vc (L) = 5.5 × BSA (m^2) and Vp = 4.1 × BSA], but even after BSA had been taken into account, the interindividual variability of the two volumes remained high (34% and 57%, respectively). The clearance (CL) was not correlated with the following covariates: age, BSA, sex, height, and levels of serum bilirubin and liver enzymes. The final regression model for CL was CL (ml/min) = 49.8 × (1 − 0.009 × PRO) × WT/Scr + 33.8 × (1 − 0.29 × META) × (1 − 0.012 × ALB), where *ALB*, *PRO*, *WT*, and *Scr*, respectively, were albuminemia, proteinemia (g/l), weight (kg), and serum creatinine (μM) and META = 1 if the patient had liver metastases (otherwise, META = 0). The interindividual variability in CL (mean value 30 ml/min) decreased only from 32% to 26% when these covariates were taken into account. The mean oral bioavailability was 66%, showing an interindividual variability of 37%. The plasma clearance of the unbound fraction was strongly and negatively correlated with Scr but was not dependent on either PRO or ALB. These data show that modifications in PRO levels do not directly affect plasma exposure to unbound etoposide. This analysis makes possible the rational consideration of modifications of covariates such as Scr in etoposide dosing. This population data base will constitute the prerequisite for adaptative control with feedback dosing for continuous oral administration of etoposide.

Key words Etoposide · Population pharmacokinetics · Unbound fraction

L. Nguyen · C. Chevreau · I. Lochon · J.-M. Bachaud
A. Pujol · P. Canal
Centre Claudius-Regaud, F-31052 Toulouse, France

B. Tranchand
Centre Léon-Bérard, Lyon, France

E. Chatelut (✉) · G. Houin · R. Bugat
Université Paul Sabatier, F-31052 Toulouse, France
Tel.: +33-5-61-42-42-71; Fax: +33-5-61-42-42-74
e-mail: chatelut@regaud-tlse.fnclcc.fr

Introduction

Etoposide, a podophyllotoxin derivative, is one of the most active antitumor agents in current clinical use. It has shown significant clinical activity against a wide variety of neoplasms, including germ-cell malignancies and small-cell lung cancer. The molecular mechanism of action of etoposide involves inhibition of topoisomerase II enzyme, the activity of which is maximal in the late G2 and S phases of the cycle. Therefore, the antitumor activity of etoposide is schedule-dependent; prolonged administration schedules have yielded a significantly higher response rate than have short-term administrations [18, 29]. Moreover, a number of reports concerning several schedules of administration show a correlation between pharmacokinetic parameters of etoposide and neutropenia, which represents its main toxicity. In most of these reports, plasma drug exposure (AUC) has been the relevant pharmacokinetic parameter [17, 23, 25]. Relationships have also been noted between the WBC nadir and the observed plasma level at 24 h after the beginning of a 3-day infusion [19, 21]. For 21-day oral treatment a relative decrease in neutrophils has been correlated with trough plasma levels of etoposide [22, 27].

Marked interpatient variability in pharmacokinetics suggests that therapeutic drug monitoring might be necessary, especially for oral etoposide. Some aspects of etoposide pharmacokinetics are well known. After i.v. dosing, plasma etoposide disappearance is biexponential, with the mean terminal half-life ranging from 3 to 12 h and not being related to the dose [14]. Etoposide plasma protein binding is extensive but varies greatly in cancer patients [20, 31]. Urinary recovery of etoposide after i.v. dosing is around 35–50%, mainly involving the unchanged form [15]. However, the part played by metabolism in the nonrenal elimination pathways is not yet clear. A recent report stated that 44% of the i.v. dose was recovered mainly unchanged in the feces, which would mean that biliary excretion is more significant than metabolism [16]. Several studies have shown modifications of etoposide pharmacokinetics in patients with organ dysfunction [1, 9, 17]. Some general initial dosing recommendations have been proposed for patients with renal impairment, such as a dose reduction of at least 30% [30]. In patients with hepatic dysfunction, no change in etoposide total clearance (CL) was reported, but the CL of free etoposide (CL_u) was decreased. Indeed, in these patients with decreased serum albumin levels, total CL was preserved due to reduced binding [32].

A population analysis using a nonlinear mixed-effects model (NONMEM) [2] was retrospectively applied to data obtained in 100 patients who had been treated for various tumor types in our center since 1986 so as to investigate in a single step the quantitative relationships between physiological features and etoposide pharmacokinetic parameters, which correspond to both total and unbound plasma concentrations in a target population.

Patients and methods

Patients' characteristics

Data on 100 unselected patients (pts; 25 women and 75 men) who had received etoposide as a part of established protocols for various tumor types in the Centre Claudius Regaud in Toulouse between 1986 and 1996 were retrospectively analyzed; 61 of them had lung cancer. The pharmacokinetic protocols were approved by the regional ethics committee. Informed consent was obtained from the patients. The characteristics of all 100 pts are summarized in Tables 1 and 2.

Etoposide dosing and analysis

Etoposide was given as i.v. (from 1-h to 72-h) infusions to 57 pts at doses ranging from 20 to 360 mg/m^2. The other 43 pts received oral etoposide during fasting (Bristol-Myers Squibb and Sandoz formulations for 20 and 23 pts, respectively), with daily doses ranging from 50 to 200 mg. Etoposide was given as a single agent to 64 pts and was combined with cisplatin for 23 pts. Samples (4 ml) were collected into tubes containing ethylenediaminetetraacetic acid (EDTA) and then separated by centrifugation, and the plasma was stored at −20 °C until analysis. A total of 1,044 samples were obtained (between 3 and 15 samples per patient over a 24-h period following the first administration).

Etoposide was assayed by reverse-phase high-performance liquid chromatography (HPLC) using teniposide as the internal standard after organic extraction according to a previously reported method [6] with ultraviolet detection at 229 nm. Intra- and interassay coefficients of variation were lower than 10%. The plasma unbound fraction (f_u) was determined in 67 pts using equilibrium dialysis [11] with tritiated etoposide (Moravek, Brea, Calif.). The characteristics of these patients with regard to albuminemia, proteinemia, and bilirubinemia were close to those of the overall population (see Table 2); median values and ranges did not differ by more than 1 unit except for the lowest value recorded for albuminemia, which was 28 g/l in this subpopulation. The radiochemical purity of the tritiated etoposide was >98%. Plasma samples collected before the administration of etoposide were dialyzed against an equal volume of Sorensen's buffer (pH 7.4) at 37 °C for 6 h. Unbound etoposide concentrations (C_u) were obtained from the product of the measured f_u and the total etoposide concentration ($C_u = f_u \times C$).

Table 1 Characteristics of the 100 patients studied

Characteristic	Number
M/F	75/25
Previous therapy with cisplatin	62
Cisplatin the day before etoposide administration	23
Diagnosis:	
Lung cancer	61
Sarcoma	6
Unknown primary	6
Lymphoma	3
Other	24
Liver metastasis	28

Table 2 Additional characteristics of the 100 patients studied

Characteristic	Median value	Range	25th–75th percentiles
Age (years)	60	25–85	52–68
Body surface area (m^2)	1.75	1.21–2.64	1.59–1.88
Weight (kg)	65	35–106	56–75
Serum creatinine (μM)	90	45–252	71–110
Creatinine clearance (ml/min)[a]	68	23–202	52–88
Creatinine clearance (ml min^{-1}1.73 m^{-2})[a]	68	20–174	54–85
Protidemia (g/l)	68	47–88	64–73
Albuminemia (g/l)	37	24–48	34–41
Bilirubinemia (μM)	9	3–32	7–11

[a] Calculated according to the Cockcroft-Gault formula [8]

Pharmacokinetic analysis

A two-compartment open pharmacokinetic model with constant-rate i.v. infusion, first-order elimination, and first-order absorption for pts receiving oral etoposide was used to describe the pharmacokinetics of total and unbound etoposide. Data were analyzed using the NONMEM program [4] (version IV, level 1.1) and the PREDPP package (ADVAN 4, TRANS 4) [3] on a Vax 6510/VMS (version V5.5) computer. A proportional-error model was used for the residual and interpatient variabilities. Unbound and total concentrations were analyzed separately.

The influence of the following covariates on the total and the unbound clearance (CL and CL_u, respectively) was examined: age, sex, weight (WT), BSA (calculated according to the Dubois formula [10]), serum creatinine (Scr), serum protein (PRO), serum albumin (ALB), total serum bilirubin, the presence of liver metastasis (META), cisplatin pretreatment (whatever the delay between cisplatin and etoposide administration), cisplatin pretreatment (when cisplatin was given the day before etoposide administration), and, for CL in 80 pts, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transpeptidase (γGT), and lactate dehydrogenase (LDH). The influence of WT, BSA, PRO, ALB, and Scr on Vc and Vp, the central volume and peripheral volume of distribution, was tested. The volume of distribution at steady state (Vdss) is equal to the sum of Vc + Vp. The influence of WT and BSA on $Vdss_u$ was tested. The influence of the oral formulation (Bristol-Myers Squib versus Sandoz) was tested on the bioavailability (F).

In fitting the data, NONMEM computed the value of a statistical function, the minimal value of objective function (OBJ), which is proportional to minus twice the log-likelihood of the data. First the population model was developed by identification of each significant covariate by its inclusion as the only covariate in the pharmacokinetic model. The objective function values were used to evaluate the increase in goodness of fit upon the inclusion of each covariate; for either of CL, Vc, and Vp a decrease in the objective function value of at least 3.8, associated with a P value of <0.05, was required to identify a covariate as being significant. Then, all significant covariates were forced into a multivariate intermediate model, and each one was eliminated in a backward stepwise approach to determine if its exclusion was statistically significant. In the evaluation of the intermediate model the objective function values were used to evaluate the decrease in goodness of fit obtained upon independent deletion of each covariate. A increase in objective function of more than 6.6, associated with a P value of <0.01, was required for retention of a covariate. Those significant covariates that remained comprised the final model.

Individual-specific true values for pharmacokinetic parameters [CL, Vc, Vp, absorption rate (Ka), lag time of absorption (lag), and coefficient of bioavailability (F)] were then obtained by Bayesian analysis using the final model with the POSTHOC option on NONMEM.

Results

Etoposide pharmacokinetic parameters

The two-compartment model with first-order absorption adequately described the plasma concentration versus time data. The linear regressions between the observed concentrations and the concentrations obtained by Bayesian pharmacokinetic analysis according to the model with a proportional-error model are shown in the inserts in Fig. 1. The residual variabilities were 17% and 15% for analyses of the total and unbound concentrations, respectively. The mean (±SD) f_u obtained by equilibrium dialysis was 8.4 ± 4.2%, ranging from 4.1% to 24.2%. The mean pharmacokinetic parameters along with their confidence intervals and their interindividual variabilities are summarized in Table 3.

Testing of the influence of covariates

The two oral formulations (Bristol-Myers Squibb and Sandoz) did not differ significantly in bioavailability (change in OBJ 2.9). Tables 4 and 5 show the increase in fit on the inclusion of each covariate and in the ratio WT/Scr. Indeed, it had previously been shown that the relationships involving the serum creatinine level for prediction of the glomerular filtration rate [8] or renal clearance of drugs [7] are improved when the body weight is taken into account. The intermediate models on CL and CL_u were built by the successive addition of each significant covariate either to the first or to the second part of the equation $CL = \theta1 \times WT/Scr + \theta2$. The covariate was kept in the intermediate only if the objective function was decreased by more than 3.8. In this procedure, age proved to be redundant with regard to WT and/or Scr. All the other covariates were retained, and the intermediate models were as follows: for total etoposide,

$$CL = \theta1 \times (1 - \theta2 \times CDDP) \times (1 - \theta3 \times PRO) \times WT/Scr + \theta4 \times (1 - \theta5 \times META) \times (1 - \theta6 \times ALB)$$

$$Vdss = \theta7 \times BSA \times (1 - \theta8/Scr),$$

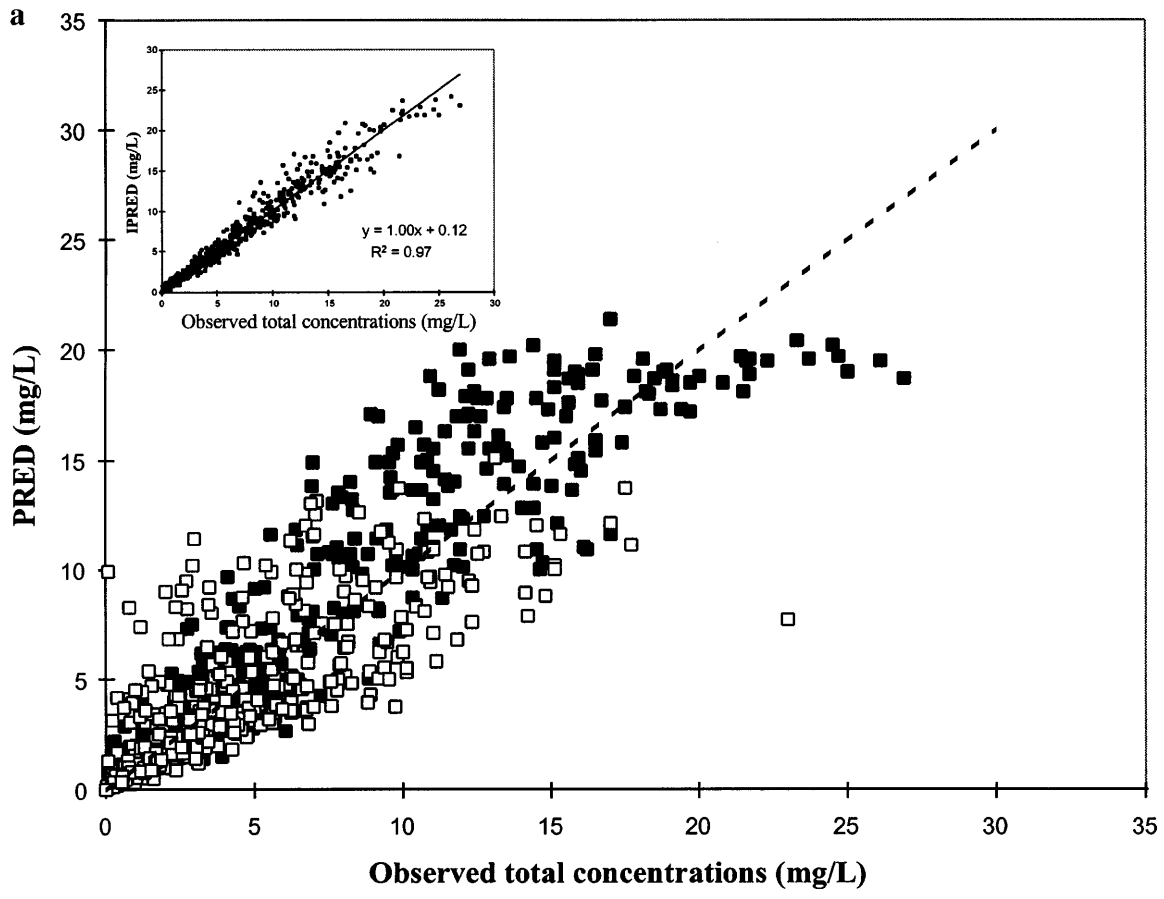
and for unbound etoposide,

$$CL_u = \theta1 \times (1 - \theta2 \times CDDP) \times WT/Scr + \theta3 \times (1 - \theta4 \times META)$$

$$Vdss_u = \theta5.$$

The final models (obtained by testing of the intermediate models against restricted models by removal of each covariate) are shown in Table 6.

In the case of the final model and parameter estimates described above, the estimate of the coefficient of variation (CV) for interindividual variability (i.e., the CV for interindividual variability not explained by the covariates included in the final model) were 26%, 34%, 57%, and 34% for CL, Vc, Vp, and CL_u, respectively. Figure 1 shows the etoposide concentrations predicted according to the final models with covariates versus observed concentrations. The mean absolute errors between the CL predicted according to the final models and the observed CL were 17% and 19%, respectively, for total and unbound etoposide. Figure 2 shows the correlation between the CL expressed as a function of significant covariates and the observed CL for total etoposide.


a
PRED (mg/L)
Observed total concentrations (mg/L)
IPRED (mg/L)
y = 1.00x + 0.12
R² = 0.97
Observed total concentrations (mg/L)

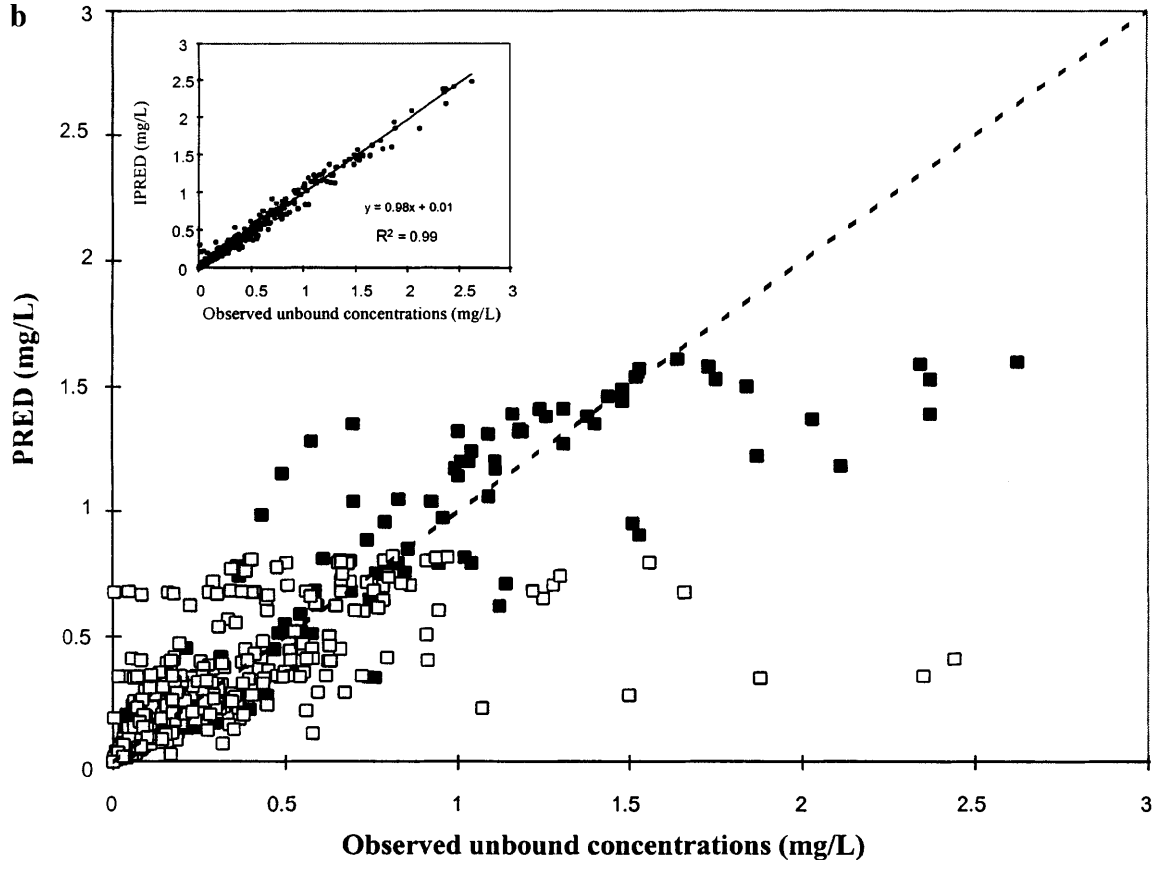

b
PRED (mg/L)
Observed unbound concentrations (mg/L)
IPRED (mg/L)
y = 0.98x + 0.01
R² = 0.99
Observed unbound concentrations (mg/L)

Table 3 Plasma pharmacokinetic parameters of total etoposide in 100 pts and unbound etoposide in 67 pts and their coefficients of variation for interindividual variability (*CL* Clearance; *Vc*, *Vp* respectively, central and peripheral volume of distribution; *Ka* rate of absorption; *lag time* lagtime of absorption; *F* coefficient of bioavailability)

	CL ml/min	Vc l	Vp l	*Ka* h^{-1}	Lag time min	F %
Total concentrations:						
Mean values	30.2	9.6	7.8	3.2	14	66
(±95% confidence interval)	(±2.9)	(±1.3)	(±1.8)	(±5.1)	(±22)	(±16)
Interindividual variability (%CV)	32	35	70	11	93	37
Unbound concentrations:						
Mean values	343	111	80	3.4	8	55
(±95% confidence interval)	(±51)	(±14)	(±25)	(±2.7)	(±13)	(±13)
Interindividual variability (%CV)	36	29	87	86	175	92

Table 4 Univariate analysis of the relationships between total etoposide pharmacokinetic parameters and patients' covariates[a] (*NS* Not significant)

Parameter investigated	Equation tested	θ2	δ	*P* (NS if $P > 0.05$)
Total clearance:				
Weight	$CL = \theta1 \times (1 + \theta2 \times WT)$		−2	NS
Body surface area	$CL = \theta1 \times (1 + \theta2 \times BSA)$		0	NS
Age (years)	$CL = \theta1 \times (1 - \theta2 \times age)$	0.005	−10	< 0.01
Sex (1 if female, 0 if male)	$CL = \theta1 \times (1 - \theta2 \times sex)$[b]		0	NS
Serum creatinine (μ*M*)	$CL = \theta1 + \theta2/Scr$	79	−40	< 0.001
Weight (kg)/Scr (μ*M*)	$CL = \theta1 + \theta2 \times WT/Scr$	1.1	−46	< 0.001
Cisplatin pretreatment	$CL = \theta1 \times (1 - \theta2 \times CIS)$	0.17	−14	< 0.001
Cisplatin pretreatment the preceeding day	$CL = \theta1 \times (1 - \theta2 \times CISp)$		−2	NS
Liver metastasis	$CL = \theta1 \times (1 - \theta2 \times META)$	0.16	−9	< 0.01
Proteinemia	$CL = \theta1 \times (1 - \theta2 \times PRO)$	0.007	−30	< 0.001
Albuminemia	$CL = \theta1 \times (1 - \theta2 \times ALB)$	0.010	−18	< 0.001
Bilirubinemia	$CL = \theta1 \times (1 - \theta2 \times BILI)$		0	NS
Each liver enzyme (ALT, AST, γGT, PAL, LDH)	$CL = \theta1 \times (1 - \theta2 \times enz)$		0	NS
Volume of distribution	(Vdss = Vc + Vp):			
Weight	$Vdss = \theta2 \times weight$	0.15, 0.12[c]	−14	< 0.001
Body surface area	$Vdss = \theta2 \times BSA$	5.6, 4.4	−26	< 0.001
Proteinemia	$Vdss = \theta1 \times (1 - \theta2 \times PRO)$		−1	NS
Albuminemia	$Vdss = \theta1 \times (1 - \theta2 \times ALB)$		0	NS
Serum creatinine	$Vdss = \theta1 \times (1 - \theta2/Scr)$	14, 30	−13	< 0.001

[a] θ2 values throughout the table are positive; δ is the difference in the objective functions
[b] The relationship with the opposite sign was also tested
[c] The first value corresponds to the central volume (e.g., $Vc = \theta2 \times WT$) and the second, to the peripheral volume (e.g., $Vp = \theta2 \times WT$)

Discussion

Many pharmacokinetics studies have been carried out on etoposide, but the present study represents the first time that concentration versus time data on both total and unbound etoposide have been analyzed with a pharmacokinetic population approach. Therefore, it was possible to assign a confidence interval to each mean pharmacokinetic parameter (e.g., the interval in which the actual mean value has a 95% probability of being present). For all parameters except the lag time of absorption these intervals were narrow, which illustrates the power of the present study. This retrospective analysis of data from 100 patients using a Bayesian approach with the NONMEM program allowed us to obtain some pharmacokinetic parameters that cannot be obtained by conventional approaches based on individual concentration-time data. The imbalance of concentration-time data among patients made individual analysis impossible for those with few samples. Moreover, data obtained after oral administration were analyzed either by a noncompartmental method or a one-compartment model [23], although etoposide pharmacokinetics after

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Fig. 1a,b Relationships between PRED, i.e., concentrations predicted according to the final models with covariates (e.g., concentrations expected if each patient had pharmacokinetic parameters corresponding to the final model) and observed concentrations for **a** total etoposide and **b** unbound etoposide. The lines of identity (- - -) are shown. ■ and □ represent concentrations obtained after i.v. and oral administration, respectively. Inserts: Relationships and regression lines (—) between IPRED, i.e., individual concentrations obtained with Bayesian pharmacokinetic analysis (with the POSTHOC option on NONMEM), and observed concentrations for **a** total etoposide and **b** unbound etoposide

Table 5 Univariate analysis of the relationships between unbound etoposide pharmacokinetic parameters and patients' covariates[a]

Parameter investigated	Equation tested	θ2	δ	P (NS if $P > 0.05$)
Unbound clearance:				
Weight (kg)	$CL = \theta1 \times (1 + \theta2 \times WT)$	0.009	−9	< 0.01
Body surface area	$CL = \theta1 \times (1 + \theta2 \times BSA)$		0	NS
Age (years)	$CL = \theta1 \times (1 - \theta2 \times age)$	0.007	−19	< 0.001
Sex (1 if female, 0 if male)	$CL = \theta1 \times (1 - \theta2 \times sex)$[b]		0	NS
Serum creatinine (μ*M*)	$CL = \theta1 + \theta2/Scr$	138	−27	< 0.001
Weight (kg)/Scr (μ*M*)	$CL = \theta1 + \theta2 \times WT/Scr$	15	−41	< 0.001
Cisplatin pretreatment	$CL = \theta1 \times (1 - \theta2 \times CIS)$	0.23	−20	< 0.001
Cisplatin pretreatment the preceding day	$CL = \theta1 \times (1 - \theta2 \times CISp)$		0	NS
Liver metastasis	$CL = \theta1 \times (1 - \theta2 \times META)$	0.26	−21	< 0.01
Bilirubinemia	$CL = \theta1 \times (1 - \theta2 \times BILI)$		−3	NS
Proteinemia	$CL = \theta1 \times (1 - \theta2 \times PRO)$[b]		0	NS
Albuminemia	$CL = \theta1 \times (1 - \theta2 \times ALB)$[b]		0	NS
Volume of distribution	(Vdss = Vc + Vp):			
Weight	$Vdss = \theta2 \times WT$		0	NS
Body surface area	$Vdss = \theta2 \times BSA$		0	NS

[a] θ2 values throughout the table are positive
[b] The relationship with the opposite sign was also tested

Table 6 Final models. Numbers in parentheses represent the 95% confidence intervals assigned to each regression coefficient[a]

Total etoposide		Unbound etoposide	
$CL = \theta1 \times (1 - \theta2 \times PRO) \times WT/Scr + \theta3 \times (1 - \theta4 \times META) \times (1 - \theta5 \times ALB)$		$CL_u = \theta1/Scr + \theta2 \times (1 - \theta3 \times META)$	
θ1	49.8 (±26)	θ1	16,233 (±3,900)
θ2	0.009 (±0.004)	θ2	190 (±100)
θ3	33.8 (±14.8)	θ3	0.49 (±0.32)
θ4	0.29 (±0.36)		
θ5	0.012 (±0.008)		
$Vdss = \theta6 \times BSA$ (Vc = θ6c × BSA, Vp = θ6p × BSA)		$Vdss_u = \theta4$ (Vc = θ4c, Vp = θ4p)	
θ6	9.6	θ4	179
θ6c	5.5 (±0.6)	θ4c	108 (±14)
θ6p	4.1 (±0.8)	θ4p	71 (±18)

[a] With META = 1 if the patient had liver metastases and otherwise, META = 0; albuminemia (ALB) and proteinemia (PRO) in g/l; WT in kg; serum creatinine (Scr) in μ*M*; and body surface area (BSA) in m^2

i.v. administration corresponds to a two-compartment model.

In this study the latter model was successfully applied to all the data. Moreover, by simultaneous analysis of i.v. and oral data, estimations of the mean bioavailability (66%) and its interindividual variability (37%) were obtained, although no patient received both i.v. and oral etoposide. This mean value confirms recent reports suggesting a bioavailability of around 60% [15]. However, our population analysis is acceptable only if the i.v. and oral groups of patients are considered as parts of the same population. The similarity of indications of these two formulations makes this assumption realistic, although the route of administration (i.v. or oral) was not randomized. The first-order absorption used in the present pharmacokinetic model accurately described the concentration versus time data. This corroborates the linear absorption observed for doses below 200 mg, when absorption of etoposide decreases between 200 and 400 mg [13].

We observed considerable interpatient variation in the protein binding of etoposide, which corresponds closely to the data obtained by Liu et al. in 36 patients [20], the mean value being 92% (range 76–96%) and 93% (range 80–97%), respectively. The ratio of 6 that we found between the highest and the lowest value for f_u had previously been reported by Stewart et al. [31]. Thus, attention must be paid to unbound plasma etoposide concentrations. Indeed, the same authors have shown a better relationship between hematologic toxicity and unbound etoposide systemic exposure as opposed to total systemic exposure [33].

With regard to the correlation between etoposide pharmacokinetic parameters and covariates, it is noteworthy that Vdss was proportional to BSA (Vdss = 9.6 l/m^2, which coincides with the median value proposed in a review on etoposide [14]), but neither CL nor CL_u was correlated with this parameter. The final models for both CL and CL_u are composed of two parts. Although it is hazardous to build physiologic theory

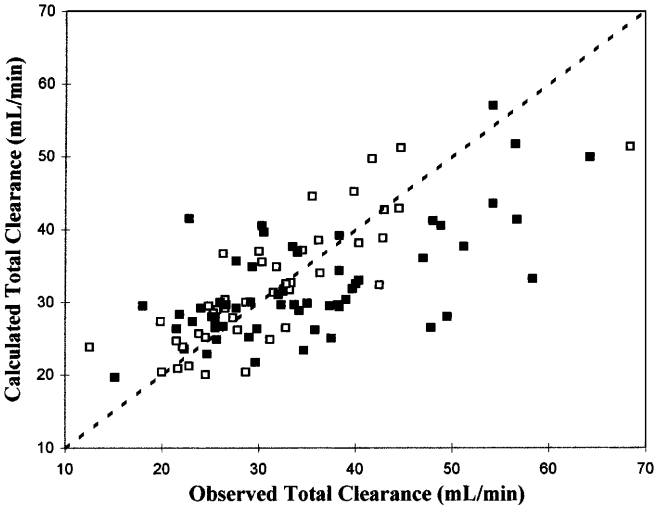

Fig. 2 Relationship between the observed etoposide clearances (obtained by Bayesian analysis using NONMEM) and the clearances calculated according to the final model with covariates. The line of identity (- - -) is shown for 100 patients treated with i.v. (■) or oral (□) etoposide

from a mathematic equation, the first part containing Scr should correspond to the renal clearance of etoposide. Indeed, by use of the final model for CL and assignment of the median value observed in this population to each covariate, values of 22 and 15 ml/min are found for renal and nonrenal clearance, respectively. The latter value coincides with the intercept of the regression line between the etoposide CL versus creatinine clearance (10 ml min^{-1} m^{-2}) found by D'Incalci et al. [9] in a population including patients with very poor renal function.

The nonrenal clearance was slightly affected by the presence of liver metastasis. Knowledge of the extent of liver involvement would probably have improved the influence of this covariate, but an accurate description of liver metastases was not available for all patients. Neither the liver enzyme nor the bilirubin levels were correlated to these parameters. Other studies have failed to find a significant correlation between liver enzymes and etoposide pharmacokinetic parameters [17, 24]. Moreover, in our population, only 1, 6, and 11 patients had serum bilirubin, ALT, and AST values, respectively, over the normal superior limit (respectively, 20 μM, 72 IU/l and 57 IU/l). The nonrenal part of CL was negatively correlated to albuminemia, but this covariate was not present in the final model on CL_u. In our population, hypoalbuminemia influences etoposide elimination not as a marker of hepatic dysfunction but by increasing the unbound etoposide plasma fraction and then increasing its total CL. Indeed, according to the venous equilibrium model [5], etoposide is a "binding-sensitive" drug. It is not surprising to obtain equivalent results for the renal part of the final models. A larger f_u due to hypoproteinemia leads to an increase in glomerular filtration of etoposide and, therefore, in CL but not in CL_u.

Prior therapy with cisplatin has previously been associated with alterations in etoposide pharmacokinetics [24]. In our study, cisplatin pretreatment was one of the factors that was significantly associated with an average reduction of 17% and 23% in CL and CL_u, respectively. However, this covariate was not present in the final models because it was redundant with other covariates. Indeed, the patients who had received prior cisplatin therapy had slightly higher Scr values (mean 98 versus 89 μM), but the difference was not significant. In patients who had received cisplatin on the day before etoposide infusion, such redundance was not expected, since Scr levels were determined before cisplatin administration. All the results would show that the nephrotoxic effect of cisplatin, which causes a decrease in etoposide clearance, seems to be more a cumulative effect than an acute interaction. In contrast, Relling et al. [26], who determined etoposide clearance three times in children who had previously been treated with cisplatin, observed mainly acute decreases in etoposide clearance when the drug was given 2 days after cisplatin.

The present study shows that renal function remains the only factor that must be taken into account for etoposide dosing. The advantage of this population approach over that applied in previous studies is that it proposes a relationship between Scr and clearance of etoposide. Therefore, in patients with high Scr values the dose reduction can be calculated rationally. Unfortunately, no covariate linked to liver function arose from the study, probably because only a few patients had altered liver function. Therefore, we cannot propose dose-adjustment guidelines for patients with biologic disorders such as high serum bilirubin levels. If the interindividual variability in CL is much lower for etoposide than for other anticancer drugs such as carboplatin [7], the interindividual variability in F probably makes oral administration the most relevant circumstance for individual dosing. We are starting to use this population data base associated with the NONMEM program to perform adaptative control with feedback dosing for continuous oral administration of etoposide. Indeed, with a limited-sampling strategy it will be possible to determine the individual pharmacokinetic parameters using a Bayesian approach. Finally, the intraindividual variability of etoposide pharmacokinetic parameters must be accurately compared with the interindividual variability, which is well described in the present report. As mentioned previously [12, 28], the intraindividual variability could limit the promising approach of individual dosing.

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