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Salivary and plasma pharmacokinetics of topotecan in patients with metastatic epithelial ovarian cancer

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Abstract

The comparative saliva/plasma pharmacokinetics of topotecan were investigated in 13 patients with metastatic epithelial ovarian cancer receiving topotecan (30-min intravenous (i.v.) infusion) on a five consecutive day schedule every 3 weeks. During the first and the second courses of treatment, each patient underwent pharmacokinetic evaluation. Quantitation of the total topotecan (lactone plus carboxylate form) was assessed by a highly specific high-performance liquid chromatographic (HPLC) method. Large patient-to-patient variations in the plasma and saliva concentrations were observed. Plasma and saliva pharmacokinetics could be described using a biexponential pattern. From the saliva data, the half-life of the terminal part of the curve was 2.64 h, it was of the same order of magnitude as the topotecan elimination half-life determined from the plasma data, 3.18 h. Topotecan concentrations were higher in the saliva than in the plasma, the saliva/plasma concentration ratio averaged 2.31 and the ratio area under the parotid saliva (AUC_s) over plasma (AUC_p) concentration–time curve (AUC_s/AUC_p) averaged 2.11. For each individual, a significant relationship was found between topotecan concentrations in the saliva and in the plasma, the coefficients of correlation ranged from 0.75 to 0.92 according to the patient. Myelosuppression, especially granulocytopenia was the most frequent toxicity encountered during the trial. The percent decrease in the leucocyte count, absolute neutrophil count and platelet count were related to the AUCp/day using sigmoidal E_{max} models. The high values of the Hill constant found reflect the very steep AUC-haematoxicity relationship observed. In most cases, abdominal pain occurred in patients presenting high saliva concentrations. One patient with high salivary concentrations (mean S/P ratio = 4.60) had grade 1 mucositis. In conclusion, the concentration of topotecan in saliva appeared to be useful as an indirect, non-invasive estimation of the levels of topotecan in the plasma; thus, saliva concentrations could be a good predictor of the behaviour of topotecan in the body. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Topotecan; Plasma; Saliva; Pharmacokinetics; Pharmacodynamics

1. Introduction

Topotecan ([S]-9-dimethylaminomethyl-10-hydroxy-camptothecin) is a semi-synthetic hydrophilic camptothecin analogue which inhibits specially the intranuclear enzyme topoisomerase I [1–3]. Compared with campthothecin, topotecan is more water soluble, has reduced protein binding, and shows promising efficacy with a strongly reduced toxicity profile [4–7]. This drug has shown anticancer activity against a variety of human tumour types, including colorectal cancer, ovarian cancer, non-small cell lung cancer and non-lymphocytic haematological malignancies [7–13]. Topotecan (Hycantin®) was approved in 1996 for the treatment of ovarian cancer following failure of first-line therapy. The main toxicity was reversible myelotoxicity, especially granulocytopenia, which was associated with thrombopenia and mucositis [6,7,14].

Topotecan exists as a pentacyclic structure with a lactone moiety in the terminal or E ring. The closed lactone ring predominates at acidic pH, but in aqueous solution, the lactone undergoes rapid and reversible pH-dependent hydrolysis to the hydroxy acid, the predominant form at physiological pH, according to a

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relatively constant ratio determined primarily by the pH [15–18]. Therefore, total topotecan concentrations (lactone plus carboxylate form) have been used to describe the pharmacokinetics of the drug, but only the closed lactone form of the drug inhibits topoisomerase I. It has been reported that measures of total plasma topotecan may be more relevant parameters for defining the pharmacological effect than a measure of the lactone form alone [18,19], which is consistent with the reversible nature of the hydrolysis of the drug.

Several studies have reported relationships between pharmacokinetic parameters (area under total plasma concentration–time curve (AUCp) and C_{max}) and haematological toxicity. Most authors have noted evidence of a dose-effect relationship for topotecan-induced myelosuppression. The sigmoidal E_{max} model provided superior fits compared with linear equations [20,21].

In clinical practice, a major advantage of the use of a saliva sample for drug monitoring instead of a blood sample is that it can be obtained non-invasively, safely and painlessly. As topotecan is not protein-bound to a great extent in plasma [6], it is theoretically an appropriate candidate for salivary investigations. Thus, in this study, the pharmacokinetic profile of topotecan (lactone plus carboxylate form) in plasma and its excretion in saliva, a route of elimination heretofore given little attention, if any, were investigated. Moreover, the relationship between topotecan plasma and salivary exposures and the occurrence of side-effects was investigated.

2. Patients and methods

2.1. Patients and eligibility criteria

Female patients with histologically-proven metastatic epithelial ovarian cancer failing treatment with a platinum- or a taxane-based chemotherapeutic regimen were included in this study. The study protocol was reviewed and approved by the institutional review board. They were performed in accordance with the Declaration of Helsinki, and with current European Community and US Food and Drug Administration guidelines for good clinical practice. All patients gave written informed consent. Complete history, physical examination, chemistry panel, complete blood count and platelet count and evaluation of the extent of tumour (using appropriate investigations) were required prior to the study entry. Eligibility criteria for the study included the following: (1) 18 years of age or older; (2) a World Health Organization (WHO) performance score of 2 or better: (3) adequate haematopoietic function (white blood cells (WBC) count $\geqslant 4\times10^9$ cells/l, absolute neutrophil count (ANC) $\geqslant 2\times10^9$ cells/l and platelet count $\geqslant 100\times10^9$cells/l).

2.2. Drug administration and doses

Topotecan (SmithKline Beecham Laboratories, France) provided as hydrochloride salt, was dissolved in 100 ml of 5% dextrose solution and administered intravenously (i.v.) by an automatic infusion pump over 30 min, repeated for 5 consecutive days every 3 weeks. At the initiation of treatment, the daily dose for the three first days corresponds to the standard recommendations (1.5 mg/m^2/day, if the patient creatinine clearance (CL_{CR} calculated according to the Cockcroft–Gault equation [22]), >0.67 ml/s; 0.75 mg/m^2/day if $0.33 \leqslant CL_{CR} \geqslant 0.67$ ml/s). The daily dose for the two last days was adjusted according to the observed area under the plasma concentration–time curve (AUCp) at day 1 [23]. During the first and the second courses of treatment, each patient underwent a pharmacokinetic evaluation.

2.3. Blood and saliva sampling

The pharmacokinetic behaviour of topotecan was assessed on days 1 and 5 of the first course of treatment, and on the first day of the second course of treatment. Both plasma and unstimulated salivary samples were collected prior to drug administration, then 25 min, 1, 1.5, 2.5, 4.5 and 8.5 h after the start of the infusion. For some patients, due to venous problems, all blood samples were not available. The duration of each salivary sampling did not exceed 2 min then the sample was immediately centrifuged at 9500*g* for 4 min. Venous blood samples were drawn into heparinised tubes. Immediately after collection, blood samples were centrifuged (1500*g*) at $+4$ °C for 10 min, then the supernatant was removed. Both plasma and salivary samples were stored at -80 °C until assay.

2.4. Haematological toxicity evaluation

To determine the haematological toxicities, patients were evaluated after each course of chemotherapy. Toxicity was defined according to the Cancer Therapy Evaluation Program Common Toxicity Criteria and graded 1–4.

2.5. Analytical method

Plasma and salivary concentrations of topotecan (lactone plus carboxylate form) were determined by a specific high-performance liquid chromatographic (HPLC) method with fluorescence detection [24]. The sample pretreatment procedure involved a protein precipitation with methanol and acidification with perchloric acid (to convert the lactone ring-opened form into its lactone form quantitatively) to quantify topotecan as a total of lactone and carboxylate forms. The

detection was performed at 361 nm for excitation and 527 nm for emission. The assay showed linearity in the tested range of 0.1–75 ng/ml. The limit of quantitation was 0.05 ng/ml. Precision expressed as percent relative standard deviation (%RSD) was in the range 0.4–17% (limit of quantitation). Accuracy ranged from 85 to 109%. Extraction recovery from the plasma or parotid saliva averaged 90%.

2.6. Pharmacokinetic analysis of plasma data

Individual pharmacokinetic parameters were estimated using an empirical Bayes methodology. Pharmacokinetic analyses were performed using the non-linear mixed-effect modelling approach as implemented in the NONMEM computer program (Version 5.0) [25] through the Visual-NM graphical interface [26]. The population characteristics of the pharmacokinetic parameters (fixed and random effects) were estimated using the First Order Conditional Estimation (FOCE) method.

As previously reported [6], an open two-compartment pharmacokinetic model with zero order input rate was used to describe the kinetics of topotecan. The four-dimensional vector θ of kinetic parameters considered in the population analysis consists of total clearance ($\theta_1 = \mathrm{Cl}$), initial volume of distribution ($\theta_2 = \mathrm{V}_1$), and the transfer rate constants ($\theta_3 = k_{12}$ and $\theta_4 = k_{21}$).

Several secondary pharmacokinetic parameters were calculated from the individual (Bayesian estimates) primary pharmacokinetic parameters: the elimination half-life ($t_{1/2}$ elim),

$$t_{1/2}\mathrm{elim} = \frac{0.693x2}{(k_{12}+k_{21}+k_{\mathrm{el}}) - \sqrt{(k_{12}+k_{21}+k_{\mathrm{el}})^2 - 4xk_{21}xk_{el}}} \quad (1)$$

with $k_{\mathrm{el}} = \mathrm{Cl}/V_1$,

the total area under the plasma concentration–time curve ($\mathrm{AUC_p} = \mathrm{dose/Cl}$) and the volume of the distribution ($V_{\mathrm{d}\beta} = \mathrm{Cl}/\beta$) where β is the elimination rate constant.

Interindividual variability was assessed according to a proportional error model associated to each fixed effect parameter, thus, for example, the clearance (Cl) of the subject j was described by the relationship:

$$\mathrm{Cl}_j = \mathrm{Cl}_{\mathrm{mean}} \cdot \exp(\eta_{\mathrm{Cl}}) \quad (2)$$

where $\mathrm{Cl}_{\mathrm{mean}}$ is the population mean and η_{Cl} is the difference between the population $\mathrm{Cl}_{\mathrm{mean}}$ and the Cl value in the subject j; η_{Cl} is assumed to be a Gaussian random variable with mean zero and variance σ^2_η. The error on the concentration measurements of the individual j was modelled by an additive model described as follows:

$$C_{ijk}(t) = f(p_j,\ D_{ij},\ t_{ij}) + \varepsilon_{1ijk} \quad (3)$$

where p_j are the pharmacokinetic parameters, t_{ij} is the time of the ith measurement, D_j is the dosing history of the subject j, f is the pharmacokinetic model, ε_{1ijk} represents the residual departure of the model from the observations and contains contributions from intraindividual variability, assay error and model misspecification for the dependent variable. ε_{1k} is assumed to be a random Gaussian variables with mean zero and variances $\sigma^2_{\varepsilon 1k}$.

The predicted serum concentrations (C_{EST}) were computed, for each individual, using the empirical Bayes estimate of the pharmacokinetic parameters using the POSTHOC option in the NONMEM program.

2.7. Pharmacokinetic analysis of the salivary data

Pharmacokinetic parameters were calculated using the Pk-fit software [27]. $C_{\max}$ is the maximum concentration in the parotid saliva. The area under the parotid saliva ($\mathrm{AUC_s}$) concentration–time curve from time zero to infinity was obtained by the linear trapezoidal approximation with correction to time infinity by dividing the last observed data point by the elimination rate constant. Elimination half-life was determined from the slope of the log linear part curves.

2.8. Pharmacokinetic–pharmacodynamic analysis

The pharmacodynamics were explored using plots of percentage decrease in red blood cells (RBC) count, WBC count, ANC count, and platelet count versus the mean AUCp/day. The percentage decrease is defined as follows: $\%\mathrm{decrease} = 100 \times (\mathrm{BV_0} - \mathrm{BV_{nadir}})/\mathrm{BV_0}$, where $\mathrm{BV_{nadir}}$ is the value of the biochemical variable at the nadir and $\mathrm{BV_0}$ is basal value. The data were modelled using a linear, a log-linear, an exponential and a sigmoidal $E_{\max}$ models. The performance of the model was evaluated by using the Akaike criterion value and the coefficient of variation on the estimated parameters.

2.9. Statistical analysis

For each individual, plasma concentrations were plotted against parotid saliva concentrations. Linear regression was performed using weighted least-squares analysis of the data (weight, $1/y^2$). The significance of the regression was confirmed using the F-test.

A regression analysis was carried out to determine the relationship between the pharmacokinetic parameters and the following covariates: age, weight, creatinine clearance and body area.

The relationship between topotecan salivary exposure and the occurrence of side-effects was investigated using the Chi-square test.

3. Results

3.1. Patient characteristics

A total of 13 patients were treated in the Medical Oncology Service of the anticancer centre of Montpellier between January 1999 and September 2000. The demographic characteristics of the patients are illustrated in Table 1. All of them had excellent performance status. Patients had a creatinine clearance (CL_{CR}) ranging from 0.42 to 2.17 ml/s.

3.2. Pharmacokinetic parameters from the plasma data

According to the patient, one (day 1 of the first course; 4 patients), two (days 1 and 5 of the first course; 3 patients) or three (days 1 and 5 of the first course and day 1 of the second course; 6 patients) kinetics were available. The topotecan plasma concentrations versus time were well described by a two-compartment model. The population database consisted of 171 topotecan concentrations. The goodness of fit has been evaluated (i) by comparing the regression line estimated on the individual predicted versus observed concentration values (slope = 0.994, standard error (S.E.) = 0.0072; intercept = 0.080 ng/ml, S.E. = 0.14) to the reference line of slope = 1 and intercept = 0 (Fig. 1); no significant difference occurred, (ii) by comparing the bias (0.015 with a 95% confidence interval of −0.15, 0.18) to zero; a *t*-test showed that this value was not statistically different from zero. The mean (±standard deviation (S.D.)) pharmacokinetic parameters are reported in Table 2. The intrapatient variability was small, with the day-to-day variations ranging from 0.5 to 15% and the course-to-course variations ranging from 1 to 25%. However, a wide interpatient variability in the pharmacokinetics of topotecan was found.

Linear regression analysis of Cl versus the creatinine clearance shows relationship with $r = 0.71$ (slope = 2.82; $P = 3.225 \times 10^{-5}$). Linear regression analysis of $V_{d\beta}$ versus the weight shows a linear relationship with $r = 0.49$ (slope = 0.75; $P = 0.0084$). The other pharmacokinetic parameters did not show a significant relationship.

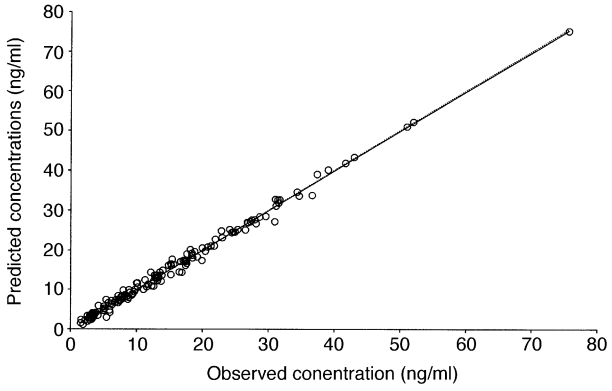

Fig. 1. Relationship between predicted (IPRED) and observed (DV) plasma concentrations. The solid line represents the linear regression line and the dotted line the line of identity.

3.3. Pharmacokinetic parameters from the salivary data

The drug concentrations versus time followed a biexponential decay pattern. Mean (±S.D.) pharmacokinetic parameters are presented in Table 2. The mean half-life of the terminal part of the curve was 2.64 h; it was of the same order of magnitude as the elimination half-life computed from the plasma data, 3.18 h. There was notable interpatient variability in the pharmacokinetics. Maximum salivary drug concentrations occurred about 1 h after drug administration, they ranged from 15 to 172 μg/l. The mean (±S.D.) S/P ratios (concentrations in saliva over those in plasma) averaged 2.31 ± 1.64. Among the 13 patients, three of them had very high salivary concentrations (S/P ratios averaging 3.0). The ratio AUC_s/AUC_p averaged 2.11 ± 1.17.

When topotecan concentrations in the saliva were plotted against topotecan plasma concentrations (Fig. 2),

Table 1
Patient characteristics

Characteristics		patients *n*
Total patients		13
Age (years)	65 (43–74)	
Weight (kg)	63 (50–89)	
Height (cm)	160 (150–165)	
Body area (m^2)	1.65 (1.45–1.96)	
Creatinine clearance		
>0.67 ml/s		9
0.33–0.67 ml/s		4
Line of chemotherapy		
Second-line		2
Third-line		9
Fourth-line		2

Table 2
Mean (± S.D.) pharmacokinetic parameters of topotecan

Pharmacokinetic parameters	Plasma data	Salivary data
C_{maxN} (μg/L)	–	93.7 ± 33.2
V_1 (L)	28.9 ± 6.79	–
Cl (L/h)	15.5 ± 4.00	–
k_{12} (h^{-1})	2.61 ± 0.12	–
k_{21} (h^{-1})	2.32 ± 0.75	–
AUC_N (μg/Lxh)	137.7 ± 35.4	271.8 ± 130.5
$t_{1/2}$elim (h)	3.18 ± 0.83	2.64 ± 1.13
$V_{d\beta}$ (L)	68.7 ± 18.7	–

S.D., standard deviation; Cl, total body clearance; V_1, initial volume of distribution; k_{12} and k_{21}, transfer rate constants; AUC, area under curve; $t_{1/2}$elim, elimination half-life; $V_{d\beta}$, volume of the distribution at the end of the distributive phase. C_{maxN} and AUC_N are normalised to a 2 mg/m^2 dose.

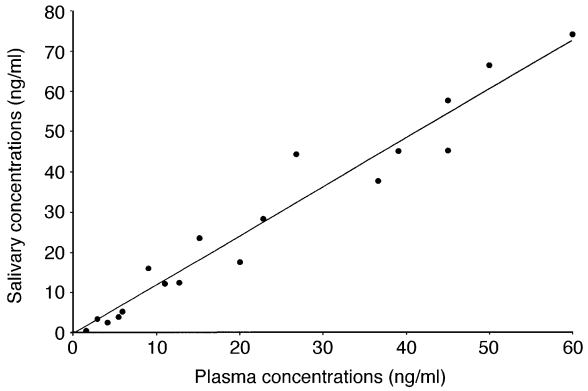

Fig. 2. Relationship between plasma and salivary topotecan concentrations in a representative patient (days 1 and 5 of the first course of treatment, and day one of the second course of treatment). Slope: 1.21; intercept: 0.16 ng/ml.

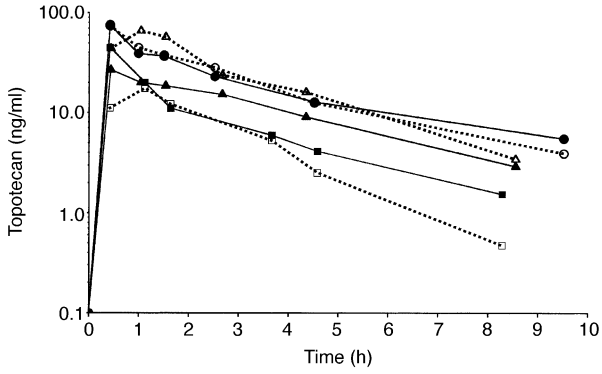

Fig. 3. Plasma and saliva concentration–time profile of topotecan after infusion of topotecan (course 1, day 1: 2.44 mg/m^2, day 5: 0.61 mg/m^2; course 2, day 1: 1.2 mg/m^2 given over 30 min) to a patient with advanced metastatic ovarian cancer. Course 1, day 1 (●) plasma, (○) saliva; course 1, day 5 (■) plasma, (□) saliva; course 2, day 1 (▲) plasma, (△) saliva.

a statistically significant straight line could be fitted to the data with coefficients of correlation ranging from 0.75 to 0.92, according to the patient. The mean slope was 2.34±1.01, and the mean intercept was 0.47 ng/ml.

Fig. 3 shows the plasma and saliva concentration versus time profiles of topotecan in a representative patient.

3.4. Haematological toxicity

In all 13 patients, the main toxicity was myelosuppression, especially granulocytopenia. The nadirs of both leucocytopenia and neutropenia were between days 8 and 17 and were of brief duration. Thrombocytopenia was much less severe. Anaemia occurred regularly. The total number of haematological toxicities encountered during this study is reported in Table 3.

3.5. Modelling the pharmacokinetic–pharmacodynamic relationship

The decrease (%) in WBC, ANC and platelet count appeared to be related to the mean AUCp/day. In all cases, the sigmoidal E_{max} model (%decrease = (ME× P^{γ})/($P_{50}^{\gamma} + P^{\gamma}$), where P represents the pharmacokinetic parameter (AUCp/day), ME denotes the asymptotic maximum effect, P_{50} is the AUCp/day value that results in a 50% decrease of the ME and γ is the sigmoidicity factor which describes the shape of the curve) produced superior fits compared with the other models (Table 4). Scatterplots of AUCp/day versus the percentage change in either WBC and ANC counts for all of the patients are presented in Fig. 4. Using this analysis, the AUCp/day producing a 50% decrease in WBC count, ANC count and platelet count was 78.9, 75.3 and 55.5 μg/l×h, respectively. The high values of the sigmoidicity factor, 3.6 and 5.8 found by plotting mean AUCp/day against the %decrease in WBC and ANC, respectively, reflect the very steep AUC–toxicity relationship observed. By plotting mean AUCp/day against the %decrease in platelet count, the sigmoidicity factor was 1.5.

4. Discussion

This study has been conducted in order to determine the pharmacokinetic profile of total topotecan (lactone plus carboxylate form) in plasma and saliva. Since this drug is poorly bound to plasma proteins only the total fraction (bound plus unbound) has been quantified in plasma. As previously reported in Ref. [6], there was substantial interpatient variability in the topotecan pharmacokinetic parameters from the plasma data, while the intrapatient variability was low. A significant relationship was found between the CL_{CR} and total plasma clearance ($r = 0.71$, $P = 3.225 \times 10^{-5}$); this result was in accordance with the results of Montazeri and

Table 3
Haematological toxicity

Course	Patients n	Leucopenia (grade)					Granulocytopenia (grade)					Thrombocytopenia (grade)					Anaemia (grade)				
		0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
1	13	0	1	4	3	5	0	1	1	3	8	5	1	1	5	1	3	5	3	2	0
2	13	0	4	4	2	3	1	3	1	3	5	9	1	1	2	0	3	3	3	4	0

Table 4
PK/PD data as a function of the various tested models

	WBC count	ANC count	Platelet count
Sigmoidal E_{max} model			
E_{max} (%)	108.3 (27.8%)	103.2 (8.3%)	98.5 (18.3%)
EC_{50} (μg×h/l)	78.9 (18.6%)	75.3 (4.2%)	55.5 (12.9%)
N	3.6 (19.9%)	5.8 (23.7%)	1.5 (29.4%)
AIC	90.3	70.7	72.2
Exponential model			
E_{max} (%)	500.4 (259.5%)	342.6 (114.6%)	119.1 (25.9%)
Alpha	0.0015 (281.2%)	0.0026 (132.4%)	0.009 (42.7%)
AIC	91.3	78.8	72.2
Linear model			
E_0 (%)	0.000421	0.000202	0.6
Slope	0.68 (13.1%)	0.78 (11.3%)	0.68 (17.3%)
AIC	91.4	84.4	78.8
Log-linear model			
E_0 (%)	0.004	0.004	0.004
Slope	15.1 (21.0%)	17.6 (15.1%)	15.4 (11.7%)
AIC	105.4	95.9	80.6

WBC, white blood cell; ANC, absolute neutrophil count; PK, pharmacokinetic; PD, pharmacodynamic; AIC, Akaike criterion. The values in parentheses are the coefficients of variation on the estimated parameters.

colleagues [23]. Moreover, a weak relationship was observed between $V_{d\beta}$ and weight ($r=0.49$, $P=0.0084$).

Since the production of saliva can be regarded as a continuous process of ultrafiltration of the plasma and as the degree of plasma protein binding of topotecan is small [6], this drug is theoretically an appropriate candidate for salivary investigations. Only van Warmerdam and colleagues [28] have studied the salivary passage of topotecan in 15 patients receiving 1.5 mg/m^2/day topotecan for 5 successive days. In this published study, citric acid was used to stimulate the saliva flow, but this saliva sampling induce mild nausea in one third of the patients. These authors have found no clear correlation between individual plasma levels and the measured saliva concentrations. However, by increasing the saliva flow, the equilibrium between plasma and saliva drug concentration can be modified. Indeed, during this study, we observed that salivary samplings during the meal must be avoided due to the increase of saliva production. Thus, in the present study, unstimulated saliva sampling was used without inconvenience for the patient. The diffusion of topotecan in the saliva was rapid; maximum salivary drug concentrations occurred about 1 h after drug administration. Topotecan concentrations were higher in the saliva compared with plasma; the saliva/plasma ratio averaged 2.31 and the ratio AUC_s/AUC_p averaged 2.11. As the carboxylate form is unlikely to cross biological barriers, the secretory mechanisms of the topotecan lactone in the saliva are not due to simple passive diffusions, but rather to active processes as previously reported for another anticancer drug, 5-fluorouracil [29]. In contrast to the results reported by van Warmerdam and colleagues [28], for each individual, there was a clear correlation between total topotecan concentrations (lactone plus carboxylate form) in the plasma and the measured saliva concentrations.

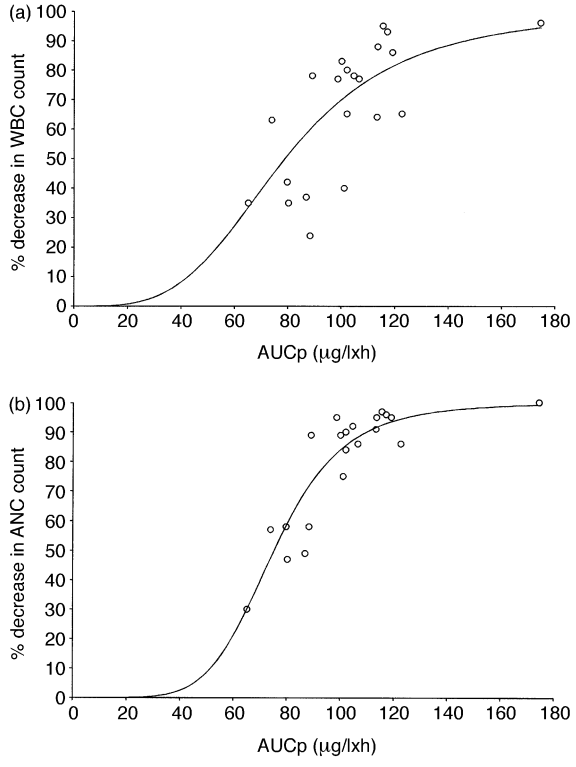

Fig. 4. Relation between the mean AUCp/day and the percent decrease in WBC count (a) and in ANC count (b). The solid lines represent the fit of the data to a sigmoidal Emax model.

Similar pharmacokinetic profiles were observed from the plasma and salivary data. Saliva pharmacokinetics can be described using a bi-exponential pattern; intra-patient variability was relatively low, but large inter-individual variability was observed. The half-life of the terminal part of the curve was 2.64 h, it was of the same order of magnitude as the topotecan elimination half-life determined from the plasma data, 3.18 h. As previously reported by van Warmerdam and colleagues [28], the saliva concentrations of topotecan were not related to the occurrence of mucositis, which was noted in only one patient. However, the occurrence of abdominal pain was observed in patients having high salivary concentrations.

The toxicity data presented in this study are consistent with those reported for the phase I and II clinical trials [6,7,14]; myelosuppression, especially granulocytopenia was the most prominent toxicity. In this study, the relationships between AUCp/day and the%decrease in WBC count, ANC count and platelet count were investigated. The pharmacodynamic-pharmacokinetic plots could be described adequately by sigmoidal E_{max} models. The high values of the Hill constant, 3.6 and 5.8, found by plotting the mean AUCp/day against the %decrease in WBC and ANC, respectively, reflect the very steep AUC–toxicity relationship observed.

In conclusion, the concentration of topotecan in the saliva appeared to be useful in indirect, non-invasive estimations of the levels of topotecan in the plasma; thus, the saliva could be a good predictor of the behaviour of topotecan in the body. In many clinical situations, including patients with difficult venous access, the determination of topotecan concentrations in the saliva may be relevant. It is reasonable to speculate that a dosage adjustment could be performed using Bayesian estimation of individual pharmacokinetic parameters based on a limited sampling strategy (for example, 5 min before the end of the 30-min infusion, and 4 h after, as previously published in Ref. [23]) and by taking into account in the final model the relationships found in this study between plasma and salivary concentrations. As large patient-to-patient variations in the S/P ratios occurred, for one of the samples, both blood and saliva could be drawn. However, these results should be confirmed in a larger population of patients.

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