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ORIGINAL ARTICLE

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Blood and plasma pharmacokinetics of vinorelbine in elderly patients with advanced metastatic cancer

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Abstract *Purpose*: As vinorelbine is 78% bound to platelets, it seems interesting to investigate the pharmacokinetic profile of this drug from blood and to compare it to that determined from plasma. Thus, in this study, the comparative blood/plasma pharmacokinetics of vinorelbine were investigated in 15 elderly patients with advanced metastatic cancer. *Methods*: The drug was given as a short (10 min) peripheral intravenous infusion; the administered dose ranged from 20 to 30 mg/m^2 depending on the patient. Chemotherapy was repeated weekly. During the first and the fifth courses, each patient underwent pharmacokinetic evaluation. Toxicity evaluation was performed after each course of chemotherapy; a total of 109 courses was studied. Plasma and blood vinorelbine determinations were performed by high-performance liquid chromatography with spectrofluorimetric detection. Individual pharmacokinetic parameters were estimated with an empirical Bayes methodology. An open three-compartment pharmacokinetic model was used to describe the kinetics of vinorelbine. *Results*: The half-lives of the terminal part of the curves, determined from blood and plasma data, were of the same order of magnitude: 31–35 h. Mean total clearances were about 0.71 l/h/kg from plasma and 0.45 l/h/kg from blood. Except during the first 15–20 min following the end of infusion, vinorelbine concentrations were 1.9 times higher in blood than in plasma. The ratio AUC_B/AUC_P (AUC_B and AUC_P are the area under the concentration–time curve from blood and plasma data, respectively) averaged 1.7; it was comparable to the blood/plasma ratio of 1.6 that remained constant over the 72 h of the study. There was substantial intra- and interpatient variability in vinorelbine pharmacokinetic parameters. This variability is similar within and between patients, and between pharmacokinetic parameters computed from blood and plasma. The elimination half-life is the parameter with the lowest intra- and interindividual variability (10–14%), while the AUC is the parameter presenting the highest variability (20–65%). The main haematological toxicity was anaemia (12 patients) and neutropenia (10 patients). Thrombocytopenia occurred in only one patient. At the first cycle, significant correlations were found between AUC_B and AUC_P and the decrease in neutrophil count ($P < 0.05$). The highest haematological toxicities encountered in this study occurred in patients presenting the lowest platelet count. AUC computed from plasma data decreased significantly with the increase of platelet count ($P = 0.03$). *Conclusion*: From the results of this study, blood did not appear to be a better predictor of haematological toxicity than plasma, but the decrease of platelet count seems to be a good predictor of this toxicity. Indeed, changes in platelet count are likely to produce strong variations in the unbound fraction of vinorelbine; this exposes the patient to a high risk of toxicity.

Keywords Vinorelbine · Blood · Plasma · Pharmacokinetics · Pharmacodynamics

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Introduction

Vinorelbine (5′-noranhydrovinblastine) is a semisynthetic antitumor drug, which has been tested against a wide variety of neoplasms. Its pharmacological effect is

potent inhibition of tubulin polymerization and weak induction of tubulin spiralization [6]. The neurotoxicity of this drug is lower than that of other vinca alkaloids, but a dose-limiting neutropenia has been reported to be relatively frequent [17]. Vinorelbine is the most lipophilic derivative of the vinca series. The pharmacokinetic profile of vinorelbine after intravenous bolus injection is characterized by high plasma clearance, a large volume of distribution, and a long terminal half-life [12]. Elimination by biliary excretion represents 70–80% of the administered dose [11]. However, there are some discrepancies in the determination of the elimination half-life and steady-state volume of distribution. The volume of distribution has been found to range from 23 to 76 l/kg, with elimination half-life values of 18–48 h [9, 13, 15, 16, 17, 18, 19, 20, 24, 25]. However, higher elimination half-lives of 56.5 and 79.8 h have been reported [2, 24]. Moreover, from in vitro experiments, Urien et al. [21] have shown that platelets are the main carrier in blood for vinorelbine; indeed, this drug is 78% platelet-bound and 14% serum-protein-bound, with 6% bound to lymphocytes and a small part bound to erythrocytes. Consequently, changes in the platelet count are likely to produce strong variations in the unbound fraction of vinorelbine in the blood.

Due to its favourable toxic profile, vinorelbine is an attractive candidate for chemotherapy in elderly patients. In a recent study, Vogel et al. [23] reported that vinorelbine appears to offer a promising alternative for the management of advanced breast cancer in elderly patients. Indeed, response rates, tolerability and dose intensity approximated that reported for women who were not age restricted. The dose-limiting toxicity was neutropenia; non-haematological toxicity was minimal. The aging process may be the cause of the reduction of hepatic clearance; however, data on vinorelbine pharmacokinetics in elderly patients are sparse [7, 20]. The preferential retention of this drug by platelets also makes it interesting to determine the pharmacokinetic profile of vinorelbine in blood.

The main objective of the present study was to investigate the pharmacokinetic profile of vinorelbine, from whole blood and plasma, in patients aged 70 years or older with metastatic cancer in progression. Individual pharmacokinetic parameters were estimated with an empirical Bayes methodology. The second objective was to acquire information regarding the tolerance to treatment in this population of patients.

Patients and methods

Patients and eligibility criteria

This study was initiated in September 1999 and was closed in February 2001. Fifteen patients aged above 70 years were enrolled in the study. Eligibility criteria for inclusion in this study were as follows: metastatic cancer in progression, histologically or cytologically proven solid tumours (of known or unknown primary site), a performance status of 3 or less on the World Health Organization (WHO) gradation scale, adequate bone marrow function (neutrophil count $\geq 1500/mm^3$, platelet count $\geq 100{,}000/mm^3$), haemoglobin levels over 10 g/dl, adequate hepatic function (bilirubin $\leq 1.5\times$ the upper normal limit, ALAT and ASAT $\leq 3\times$ the upper normal limit), and adequate renal function (creatinine clearance > 50 ml/min).

The study protocol was reviewed and approved by the institutional review board. It was performed in accordance with the Declaration of Helsinki, and according to European Community and U.S. Food and Drug Administration guidelines for good clinical practice. The patients were fully informed about the procedure and the purpose of the experiment, and gave written consent.

Treatment regimen and blood sampling

All the patients received single-agent vinorelbine therapy. The drug was given as a short (10 min) peripheral intravenous infusion in 100 ml normal saline solution. The administered dose was 20–30 mg/m^2. Depending on the patients, premedication consisted of dexamethasone or methylprednisolone, metoclopramide or ondansetron.

Vinorelbine was administered on a weekly basis and continued until progression of disease, severe toxicity, or patient refusal. For each patient, the administered dose remained constant during the treatment period. Pharmacokinetics was performed after the first and the fifth cycle.

Two blood samples were drawn in heparinized glass tubes at the end of infusion, and 20 min, 1, 6, 12, 18, 24, 48, and 72 h after the start of infusion. Immediately after collection, to separate the plasma, one sample was centrifuged (1500*g* for 10 min) at 4 °C. Blood and plasma samples were kept frozen (–20 °C) until analysis.

Toxicity evaluation

Adverse effects, chemistry panel and complete blood cell count including differential white blood cell count and platelet count were determined after each course, to evaluate possible bone marrow, renal, or liver toxicity. Physical examination, vital signs, and performance status were re-evaluated every 4 weeks. Toxicity was defined according to the Cancer Therapy Evaluation Program common toxicity criteria and graded 1 to 4.

Analytical method

Vinorelbine concentrations in plasma and blood were assayed by high-performance liquid chromatography with spectrofluorimetric detection [8]. The detection was performed at 280 nm for excitation and at 360 nm for emission. After addition of an internal standard (vinblastine) to the samples to be analyzed, the extraction procedure involved two liquid–liquid extraction steps. The assay showed linearity from 1 to 100 ng/ml in plasma and from 2.5 to 100 ng/ml in blood. The limits of quantitation were 1 ng/ml and 2.5 ng/ml in plasma and blood, respectively. Precision was in the range 3.9 to 20% (limit of quantitation). Accuracy ranged from 92 to 120%.

Population pharmacokinetic analysis

For some patients, due to venous problems, all blood samples were not available; thus the classical pharmacokinetic approach was not possible. Consequently, individual pharmacokinetic parameters were estimated with the use of an empirical Bayes methodology.

Pharmacokinetic analyses were performed by the non-linear mixed-effect modelling approach as implemented in the NONMEM computer program (Version 5.0) [1] through the Visual-NM graphical interface [22]. Blood and plasma data were analysed separately. In both cases, the population characteristics of the pharmacokinetic parameters (fixed and random effects) were estimated by use of the first-order conditional estimation (FOCE) method.

As previously published [7, 8], an open three-compartment pharmacokinetic model with zero-order input rate was used to

describe the kinetics of vinorelbine. The six-dimensional vector θ of the kinetic parameters considered in the population analysis consisted of total body clearance (CL), initial volume of distribution (V_1), the transfer rate constants (k_{21} and k_{31}), the distribution rate (α), and the elimination rate (β).

Several secondary pharmacokinetic parameters were calculated from the individual (empirical Bayes estimates) primary pharmacokinetic parameters: the area under the concentration–time curves (AUC_B from blood data, AUC_P from plasma data) were computed as AUC = dose/CL; the elimination half-life ($t_{1/2elim}$) was computed as $t_{1/2elim} = 0.693/\beta$ and the volume at the end of the distributive phase ($V_{d\beta}$) was calculated as $V_{d\beta} = CL/\beta$. Different models for inter- and intraindividual variabilities have been tested (additive, proportional). The model has been chosen on the basis of the quality of fit and of the dispersion of the standardized residuals (not shown).

The general statistical model for interindividual variability in pharmacokinetic parameters was the following:

$$P_j = P_{mean} \cdot \exp(\eta_{jP}) \quad \text{(a)}$$

where P is one of the pharmacokinetic parameters (CL, V_1, k_{21}, k_{31}, α, β), P_{mean} is the population mean and η_{jP} denotes the (proportional) difference between the population mean P_{mean} and the estimated value of P in subject j (P_j). The random variable η_{jP} is distributed with a mean of zero and variance of ω_P^2. The error in the concentration measurements of individual j was modelled by a combined additive and proportional model described as follows:

$$C_{ijk}\ (t) = f(P_j,\ D_{ij},\ t_{ij}) \cdot\ exp(\varepsilon_{1ijk}) + \varepsilon_{2ijk} \quad \text{(b)}$$

where C_{ijk} is the measured vinorelbine concentration, P_j is the pharmacokinetic parameter, t_{ij} is the time of the ith measurement, D_j is the dosing history of subject j, f is the pharmacokinetic model, ϵ_{1ijk} and ϵ_{2ijk} represent the residual departure of the model from the observations, containing contributions from intraindividual variability, assay error, and model misspecification for the dependent variable. Variables ϵ_{1k} and ϵ_{2k} are assumed to be randomly Gaussian with means of zero and variances of $\sigma^2_{\varepsilon 1k}$ and $\sigma^2_{\varepsilon 2k}$, respectively.

The predicted concentrations (IPRED) were computed, for each individual, by the empirical Bayes estimate of the pharmacokinetic parameters and with the POSTHOC option in the NONMEM program.

Model acceptance

To judge the adequacy of the model to the data, graphics and descriptive statistics were used. Individual predicted concentrations (IPRED) were plotted versus observed concentrations (DV), and the results were compared to the reference line with slope = 1 and intercept = 0.

To compare observed concentrations (DV) to the ones estimated with the Bayesian approach (IPRED), the bias or mean predictor error was computed as follows:

$$\text{Bias} = \frac{1}{N}\sum_{i=1}^{i=N} [\text{DV} - \text{IPRED}] \quad \text{(c)}$$

In this expression, index i refers to the concentration number, and N is the sample size. The confidence interval for bias was also computed. The t test was used to compare the bias to zero.

Statistical analysis

Regression analyses were carried out to determine the relationship between patient variables (age, weight, and body area) and pharmacokinetic parameters (CL, $t_{1/2elim}$, AUC, $V_{d\beta}$) computed from both blood and plasma data.

As vinorelbine is preferentially bound to platelets, regression analysis was carried out to determine the relationship between the number of platelets and AUC_P.

After the first course of chemotherapy, the dose-limiting toxicities were explored by use of plots of percentage decrease in haemoglobin and absolute neutrophil count (ANC) versus AUC (AUC_P and AUC_B) and the concentration of vinorelbine at the end of infusion (both from blood and plasma). For this purpose, the measured haematological variable (HV) was transformed with the use of the percentage change (D%) from the basal value (HV_0); this was computed as follows: $D\% = 100\times(HV_0 - HV_{min})/HV_0$, where HV_{min} is the minimum value of the haematological variable between the two first courses.

The appropriateness of the linear model was assessed by a test for "lack of fit" in conjunction with the test of a slope different from zero [4]. To perform this analysis, the computer program Pk-fit was used [5, 14]. Significance was assessed at the α level of 0.05.

Results

Patient characteristics

Fifteen elderly patients (9 female and 6 male subjects) were enrolled in this trial and admitted to the Medical Oncology Service of the Anticancer Center (Montpellier, France). The primary tumour types were ovarian carcinoma (1 patient), non-small cell lung cancer (3 patients), breast cancer (4 patients), prostate cancer (2 patients), kidney cancer (1 patient), and head and neck cancer (1 patient). Three patients had adenocarcinoma of unknown primary. Among the patients, seven had received prior chemotherapy, six had received prior hormone therapy, and six had prior radiotherapy. Three patients had prior surgery. The WHO performance status scores were 0 (1 patient), 1 (7 patients), 2 (5 patients), and 3 (2 patients).

The patients received between 2 and 20 courses of chemotherapy. Their average age was 73.5 years (71 to 80 years) and their average weight was 65.8 kg (44 to 94 kg). No patient received granulocyte colony-stimulating factor. Six patients were entered into the study at the 20-mg/m^2 dose level, three at the 22.5-mg/m^2 dose level, five at the 25-mg/m^2 dose level, and one at the 30-mg/m^2 dose level.

Toxicity

All patients were assessable for toxicity (109 courses). No patient required a dose reduction. Pre-study neutrophil, platelet, and haemoglobin levels were within the normal range. Two patients received two courses (weekly dose, 25 and 30 mg/m^2), two patients received three courses (weekly dose, 20 and 25 mg/m^2), one patient received four courses (weekly dose, 25 mg/m^2), one patient received five courses (weekly dose, 20 mg/m^2), four patients received six courses [weekly dose, 25 mg/m^2 (2 patients), 22.5 mg/m^2 (2 patients)], four patients respectively received 8, 12, 16, and 20 courses (weekly dose, 20 mg/m^2), and one patient received ten courses (weekly dose, 22.5 mg/m^2). The predominant toxicities were anaemia and neutropenia (Table 1). Anaemia and

Table 1 Haematological toxicity

Dose (mg/m^2)	No. of patients	No. of courses	No. of courses[a]									
			Anaemia WHO grade					Neutropenia WHO grade				
			0	1	2	3	4	0	1	2	3	4
20	6	64	43	20 (3)	1			47	12	5 (2)		
22.5	3	22	15	3	4			11	1	3	2	5
25	5	21	7	7	5 (1)	2		14	2	2	2	1
30	1	2				2						2

[a]Values in parentheses are the toxicity cases during the first course

neutropenia occurred in 40 and 34% of courses, respectively. Neutropenia WHO grades 3 and 4 were observed in 4 courses (4 patients) and 8 courses (3 patients), respectively, of 109 assessable courses. Neutropenic fever, requiring intravenous antibiotics, occurred in 3 patients (3 courses); in one case, fever episodes were bacteriologically documented (*Escherichia coli*). Grade 3 anaemia was observed in 4 courses (3 patients) and required packed red blood cell transfusion in three instances. Five patients (47 courses) had no neutropenia and three patients (24 courses) had no anaemia.

Thrombocytopenia was not significant; grade 2 was observed in 1 patient (2 courses) without need for platelet transfusion.

Non-haematological toxicities consisted predominantly of asthenia (grade 1–2, 7 patients, 13 courses), nausea and vomiting (grade 1, 3 patients, 3 courses; grade 3, 2 patients, 3 courses), diarrhoea (grade 1, 1 patient, 1 course), constipation (grade 2, 3 patients, 3 courses) and alopecia (grade 1, 1 patient, 1 course; grade 3, 1 patient, 1 course). Some types of antiemetic medications were used, ondansetron in one patient and metoclopramide in 2 patients. No stomatitis was reported. Eight patients had no extramedullary toxicity.

There was no evidence of a relationship between severe haematological toxicity incidence and cumulative treatment dose.

Pharmacokinetic parameters

Complete plasma and blood concentration versus time plots (two courses) were obtained for 8 patients. For the other patients, only the kinetic measurements performed on the first day of treatment was available. The full population pharmacokinetic profile achieved by varying the sampling scheme across patients is illustrated in Fig. 1A for blood and in Fig. 1B for plasma. The population data base consisted of 165 vinorelbine concentrations. The population parameters are given in Table 2. The goodness of fit was evaluated by (a) comparison of the respective regression lines for blood and plasma of the predicted versus observed concentration values to a reference line with slope = 1 and intercept = 0 [blood data (A): slope 0.997 (SE 0.0062), intercept 4.16 ng/ml (SE 2.35); plasma data (B): slope 1.00 (SE 0.0069), intercept 3.61 ng/ml (SE 2.56)] (Fig. 2); there was no significant difference; (b) comparison of the bias (blood data: –3.53 ng/ml, 95% confidence interval: –7.7 to 0.66; plasma data: –4.3 ng/ml, 95% confidence interval: –8.9 to 0.29) to zero; the *t* test showed that the bias values were not statistically different from zero. The mean (± SD) pharmacokinetic parameters determined after the first course of chemotherapy are reported in Table 3. The half-lives of the terminal part of the curves, determined from blood and plasma data, were of the same order of magnitude (31–35 h). In most patients, the vinorelbine concentrations were higher in the blood than in the plasma.

The mean (± SD) blood/plasma concentration ratio of vinorelbine averaged 1.9 ± 1.1. The ratio AUC_B/AUC_P averaged 1.7 (CV = 41%); it was comparable to the B/P ratio of 1.6 estimated from the haematocrit value (35.0 ± 3.4%), which remained constant over the 72 h of the study.

In eight patients, the pharmacokinetic parameters were determined twice at 1-month intervals (courses 1 and 5). Both from blood and plasma, the intrapatient variability in the elimination half-life was small, with the course-to-course variations ranging from 0.4 to 25%, while the intrapatient variability in CL, AUC, and $V_{d\beta}$ was higher at 2.7–55%, 2.8–55%, and 10–53%, respectively. Figure 3 shows the plasma and blood concentration versus time profiles of vinorelbine in a representative patient.

Statistical analysis

A significant relationship was found between the $V_{d\beta}$ determined from plasma data and the body area ($P = 0.0357$). The other pharmacokinetic parameters did not show significant correlation with any body parameters.

Vinorelbine AUC at first cycle was significantly correlated with the decrease in ANC ($r = 0.6$, $P = 0.028$ from plasma data; $r = 0.54$, $P = 0.0376$ from blood data). AUC was the only measure of vinorelbine exposure to reach statistical significance.

AUC computed from plasma data decreased significantly with the increase of platelet count ($P = 0.03$).

Discussion

From in-vitro experiments, it has been shown that platelets are the main carrier in blood for vinorelbine [21]; thus, pharmacokinetic parameters computed from blood could be a better predictor of the occurrence of side effects or of the efficacy of this drug than those computed from plasma. To our knowledge, this is the first study that provides detailed information about vinorelbine pharmacokinetic behaviour in blood. In addition, assessment of inter- and intra-patient variability of pharmacokinetic parameters is thought to be of central importance to establish optimal and safe dosage recommendations by the clinician.

Cancer management in the older patient is a growing concern, particular with the increasing geriatric population and the high incidence of cancer among these individuals. Thus, in the present study, the pharmacokinetic profiles of vinorelbine, from blood and plasma data, were studied in fifteen elderly patients with advanced metastatic cancer. For eight of them, pharmacokinetics were performed twice at 1-month intervals. There are only a few studies reporting the pharmacoki-

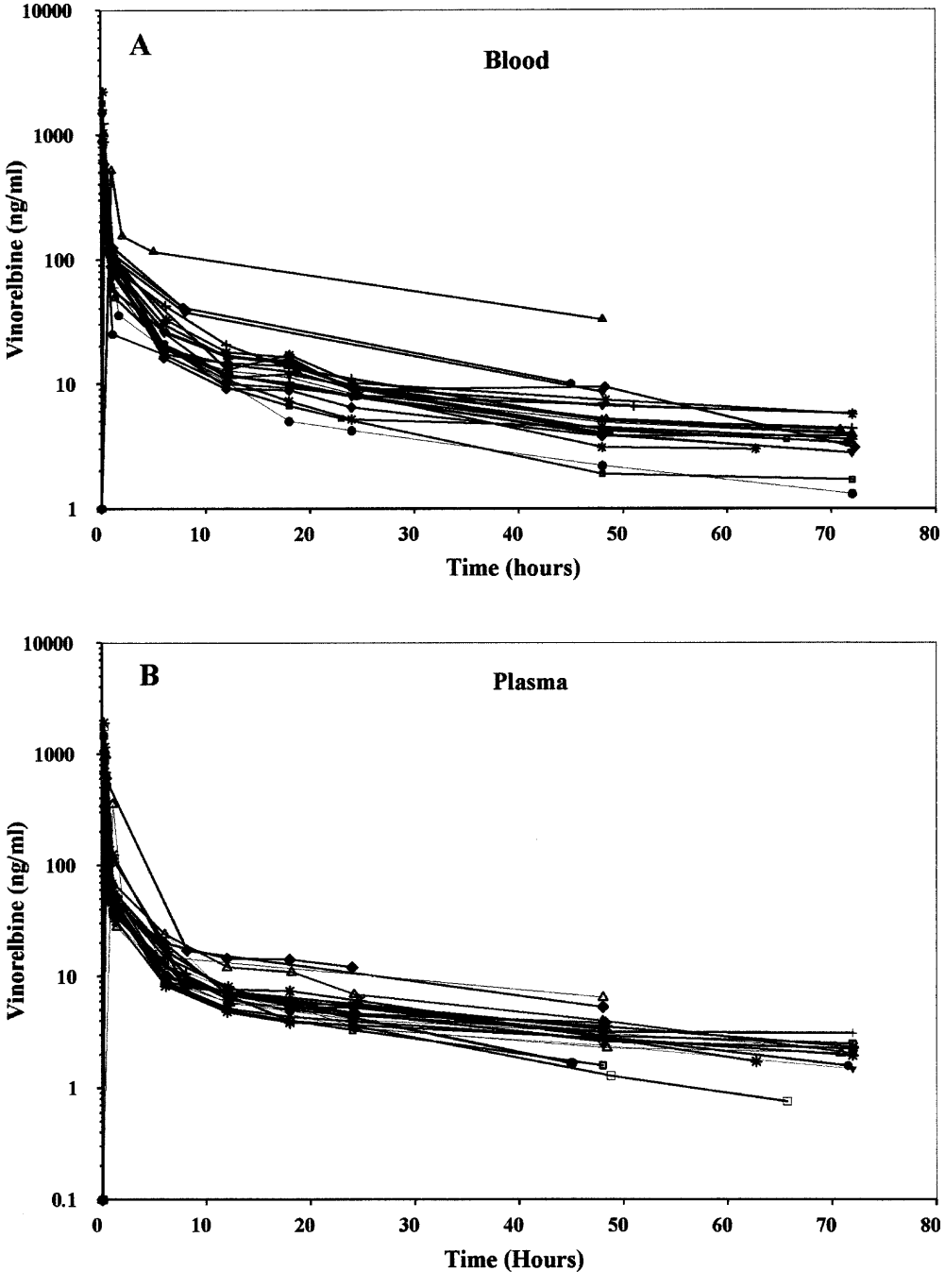

Fig. 1 Vinorelbine population pharmacokinetic profile in blood (**A**) and plasma (**B**)

Table 2 Population pharmacokinetic parameters of vinorelbine

Parameters	Plasma		Blood	
	Population mean	Interindividual variability, CV%	Population mean	Interindividual variability, CV%
V (l)	17.9	75.4	16.3	55.6
CL (l/h)	43.8	24.0	27.4	29.1
α (h^{-1})	0.426	8.85	0.355	22.9
β (h^{-1})	0.0202	15.3	0.0228	11.9
k_{21} (h^{-1})	0.662	7.59	0.824	23.7
k_{31} (h^{-1})	0.0399	20.6	0.0556	9.65
Residual intraindividual coefficient of variability	$\sigma_{\epsilon 1}$: 8.8%; $\sigma_{\epsilon 2}$: 37.7%		$\sigma_{\epsilon 1}$: 6.5%; $\sigma_{\epsilon 2}$: 21.1%	
Objective function	756.9		981.4	

CL, total body clearance; V, initial volume of distribution; k_{21} and k_{31}, transfer rate constants; α, distribution rate; β, elimination rate

netic behaviour of vinorelbine in aging patients [7, 20]. Since the liver and renal functions might be altered in this patient population, such modifications could alter the pharmacokinetics. For some patients included in this study, due to venous problems, only sparse samples are available; thus classical compartmental or non-compartmental analysis could not be done to compute individual pharmacokinetic parameters. Therefore, an empirical Bayes methodology was used. In this analysis, population characteristics of the parameters to be estimated were used as prior information to estimate each of the individual pharmacokinetic parameters. Moreover, such an approach avoids a possible bias in the estimation of the elimination half-life (i.e., underestimation) when the last sampling time (i.e., 72 h) cannot be obtained [7].

Blood and plasma concentration versus time curves were similar enough (Fig. 3); the kinetic profiles were triphasic. The elimination half-lives from plasma and blood data were of the same order of magnitude, 31–35 h. Total plasma clearance was high (0.75 ± 0.20 l/min). Assuming a hepatic blood flow in the human of 1.5 l/min, vinorelbine total plasma clearance was about half the rate of hepatic blood flow. Vinorelbine concentrations were 1.9 times higher in blood than in plasma, except during the first 15–20 min following the end of infusion. These results are in agreement with the conclusion of Urien et al. [21], that the fast distribution phase observed in the plasma pharmacokinetics of vinorelbine could be related to its rapid uptake in platelets and white blood cells. The ratio AUC_B/AUC_P averaged 1.7; it is comparable to the blood/plasma ratio of 1.6 that remained constant over the 72 h of the study. There was substantial intra- and interpatient variability in vinorelbine pharmacokinetic parameters. This variability was quite similar, on the one hand, within and between patients, and, on the other hand, from blood or plasma data. The elimination half-life is the parameter presenting the lowest intra- and interindividual variabilities: 10–14%, while AUC is the parameter with the highest intra- and interindividual variability (20–65%). Pharmacokinetic parameters computed from plasma data were in accordance with our previous study carried out in elderly patients [7]. A weak relationship was found between $V_{d\beta}$ determined from plasma data and the body area ($P = 0.0357$). The other pharmacokinetic parameters did not show any significant relationships.

In this paper, a total of 109 vinorelbine cycles were studied. The main haematological toxicities were neutropenia and anaemia. Neutropenia and anaemia WHO grades 3 and 4 occurred in a small number of courses ($< 10\%$). Neutropenia and anaemia were not observed in five (47 courses) and three patients (24 courses), respectively. Thrombocytopenia was infrequent (1 patient). Five patients (17 courses) required a treatment delay (1 to 3 weeks). There was one episode of grade 3 alopecia. Grade 3 nausea and vomiting occurred in only two patients. No injection site reactions occurred, which is consistent with a previous report showing that rapid infusion minimizes venous irritation [3].

Pharmacodynamic data relative to vinorelbine are scarce. From the relationship between AUC and the percent decrease in ANC found in the present study, vinorelbine exposure appeared to be a significant predictor of neutropenia. This result confirms our previous findings [7] and were in good agreement with those of Khayat et al. [10]; indeed, these authors found that a higher systemic exposure results in a higher risk for severe haematological toxicity. The highest haematological toxicity encountered in this study occurred in patients presenting the lowest platelet count, and a significant relationship was found between platelet count and the percentage decrease in ANC ($P = 0.0105$). Moreover, AUC computed from plasma data decreased significantly with the increase of platelet count ($P = 0.03$).

In conclusion, the blood and plasma pharmacokinetic profiles of vinorelbine are quite similar, with blood concentrations about 1.9 times higher than plasma concentrations. From the results of this study, blood did not appear to be a better predictor of haematological toxicity than plasma, but the decrease of platelet count should be a good predictor of this toxicity. Indeed, changes in platelet count are likely to produce strong

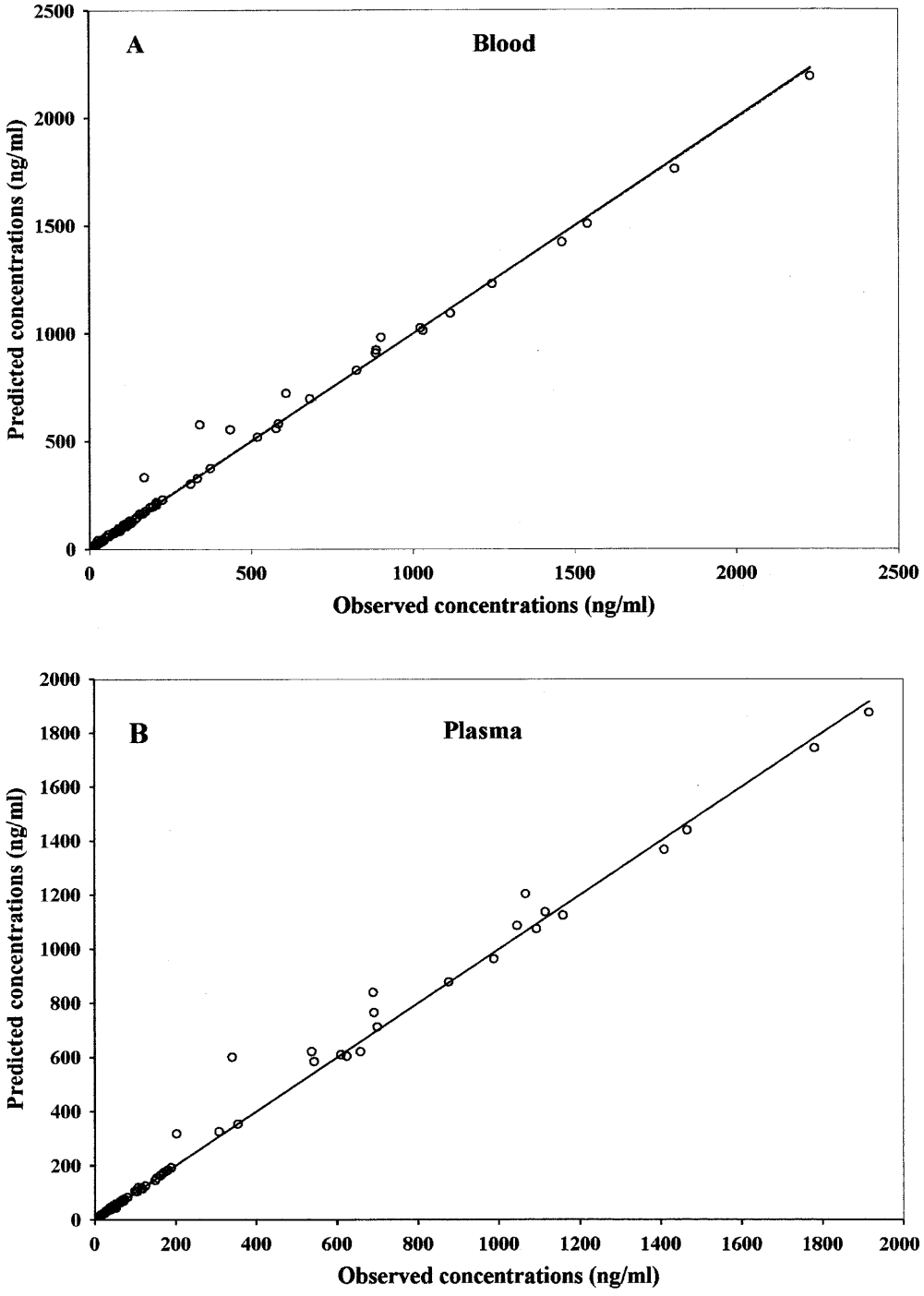

Fig. 2 Relationship between predicted (IPRED) and observed (DV) plasma concentrations in blood (**A**) and plasma (**B**). The *solid line* represents the linear regression line and the *dotted line* the line of identity

Table 3 Mean (± SD) pharmacokinetic parameters of vinorelbine computed from the first courses of chemotherapy

	Plasma	Blood
CL (l/h) range	45.1 ± 12.2 (21.6–75.9)	27.7 ± 9.25 (7.38–45.8)
CL (l/h/kg) range	0.722 ± 0.194 (0.432–1.05)	0.447 ± 0.176 (0.16–0.88)
$t_{1/2elim}$ (h) range	35.0 ± 5.05 (25.4–43.2)	30.9 ± 4.35 (23.0–40.7)
AUC (μg h l^{-1}) range	896 ± 226 (594–1451)	1653 ± 1067 (656–5116)
$V_{d\beta}$ (l) range	2258 ± 659 (1238–3677)	1215 ± 394 (434–1889)
$V_{d\beta}$ (l/kg) range	36.1 ± 9.55 (21.0–51.1)	19.5 ± 7.09 (36.3–9.43)

CL, total clearance; $t_{1/2elim}$, half-life of elimination; AUC, area under the concentration–time curve; $V_{d\beta}$, apparent volume of distribution

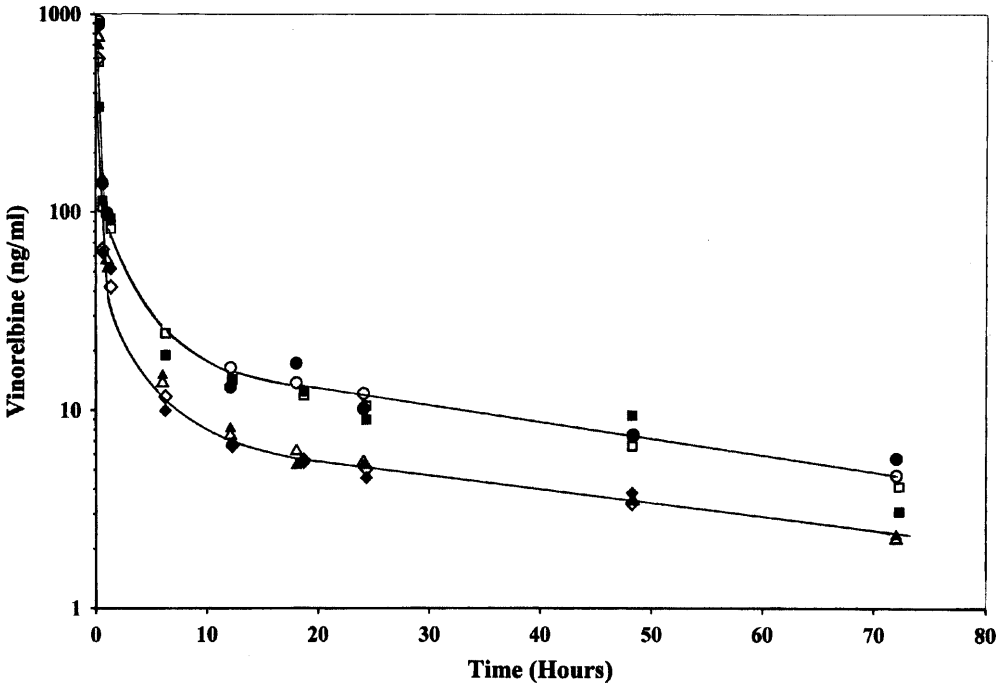

Fig. 3 Blood and plasma concentration–time profile of vinorelbine in a representative patient. Cycle 1. Blood: ■ DV; □ IPRED. Plasma: ◆ DV; ◇ IPRED. Cycle 5. Blood: ● DV; ○ IPRED. Plasma: ▲ DV; Δ IPRED

variations in the unbound fraction of vinorelbine, exposing the patient to a high risk of toxicity.

References

1. Beal SL, Sheiner LB (1992) NONMEM User's Guide, University of California at San Francisco, San Francisco
2. Boré P, Rahmani R, van Cantfort J, Focan C, Cano JP (1989) Pharmacokinetics of a new anticancer drug, Navelbine, in patients. Cancer Chemother Pharmacol 23: 247
3. Cinieri S, Orlando L, Cocorocchio E, Munzone E, Catania C, Brunetti C, Rocca A, Martinelli G, Nole F (1999) Prophylaxis of toxic effects on the peripheral venous system associated with intravenous administration of vinorelbine. Clin Ther 150: 225
4. Draper NR, Smith H (1966) Applied Regression Analysis. Wiley, New York
5. Farenc C, Fabreguette J, Bressolle F (2000) Pk-fit: a pharmacokinetic/pharmacodynamic and statistical data analysis software. Comput Biomed Res 33: 315
6. Fellous A, Ohayon R, Vacassin T, Binet S, Lataste H, Krikorian A, Couzinier JP, Meininger V (1989) Biochemical effects of Navelbine on tubulin and associated proteins. Semin Oncol 16(Suppl 4): 9
7. Gauvin A, Pinguet F, Culine S, Astre C, Gomeni R, Bressolle F (2000) Pharmacokinetic parameters of vinorelbine in elderly patients with advanced metastatic cancer. Clin Cancer Res 6: 2690
8. Gauvin A, Pinguet F, Poujol S, Astre C, Bressolle F (2000) High-performance liquid chromatographic determination of vinorelbine in human plasma and blood: Application to a pharmacokinetic study J Chromatogr B 748: 389
9. Jehl F, Quoix E, Levêque D, Pauli G, Breillout F, Krikorian A, Monteil H (1991) Pharmacokinetic and preliminary metabolic fate of Navelbine in humans as determined by high performance liquid chromatography. Cancer Res 51: 2073
10. Khayat D, Covelli A, Variol P, Benhamouda A, Jacques C, Bugat R (1995) Phase I and pharmacologic study of intravenous vinorelbine in patients with solid tumors (abstract). J Clin Oncol 14: 469
11. Krikorian A, Rahmani R, Bromet M, Boré P, Cano JP (1989) Pharmacokinetics and metabolism of Navelbine. Semin Oncol 16(Suppl. 4): 21
12. Levêque D, Jehl F (1996) Clinical pharmacokinetics of vinorelbine. Clin Pharmacokinet 31: 184
13. Marquet P, Lachatre G, Debord J, Eichler B, Bonnaud F, Nicot G (1992) Pharmacokinetics of vinorelbine in man. Eur J Clin Pharmacol 42: 545
14. Pk-fit Computer Program (1999) Version 2.1, R.D.P.P., Montpellier, France.
15. Rahmani R, Bruno R, Iliadis A, Favre R, Just S, Barbet J (1987) Clinical pharmacokinetics of the antitumor drug Navelbine (5′-Noranhydrovinblastine). Cancer Res 47: 5796
16. Rahmani R, Gueritte F, Martin M, Just S, Cano JP, Barbet J (1986) Comparative pharmacokinetics of antitumor vinca alkaloids: intravenous bolus injections of Navelbine and related alkaloids to cancer patients and rats. Cancer Chemother Pharmacol 16: 223
17. Robieux I, Sorio R, Borsatti E, Cannizaro R, Vitali V, Aita P, Freschi A, Galligioni E, Monfardini S (1996) Pharmacokinetics of vinorelbine in patients with liver metastases. Clin Pharmacol Ther 59: 32
18. Rowinsky EK, Noe DA, Trump DL (1994) Pharmacokinetic, bioavailability, and feasibility study of oral vinorelbine in patients with solid tumours. J Clin Oncol 12: 1754
19. Sabot C, Marquet P, Debord J, Carpentier N, Merle L, Lachâtre G (1998) Bayesian pharmacokinetic estimation of vinorelbine in non-small-cell lung cancer patients. Eur J Clin Pharmacol 54: 171
20. Sorio R, Robieux I, Galligioni E, Freschi A, Colussi AM, Crivellari D, Saracchini S, Monfardini S (1997) Pharmacokinetics and tolerance of vinorelbine in elderly patients with metastasic breast cancer. Eur J Cancer 33: 301
21. Urien S, Brée F, Breillout F, Bastian G, Krikorian A, Tillement JP (1993) Vinorelbine high-affinity binding to human platelets and lymphocytes: distribution in human blood. Cancer Chemother Pharmacol 32: 231
22. Visual-NM User's manual (1998) Version 5.1, R.D.P.P., Montpellier, France
23. Vogel C, O'Rourke M, Winer E, Hochster H, Chang A, Adamkiewicz B, White R, McGuirt C (1999) Vinorelbine as

first-line chemotherapy for advanced breast cancer in women 60 years of age or older. Ann Oncol 10: 397
24. Zhou XJ, Boré P, Monjanel S, Sahnoun Z, Favre R, Durand A, Rahmani R (1991) Pharmacokinetics of Navelbine after oral administration in cancer patients. Cancer Chemother Pharmacol 29: 66
25. Zhou XJ, Zhou-Pan XR, Favre R, Rahmani R (1994) Relative bioavailability of two oral formulations of Navelbine in cancer patients. Biopharm Drug Dispo 15: 577