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Pharmacokinetics of navelbine after oral administration in cancer patients*

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Summary. The pharmacokinetic behavior of navelbine was investigated in 19 patients presenting with advanced cancers (mainly women with breast cancer). Navelbine was given orally at seven dose levels of up to 200 mg/week. For a given dose, patients received four successive weekly treatments. Five subjects also received two different doses. After drug administration, plasma was collected for 48 or 72 h and monitored for navelbine concentration by radioimmunoassay. Absorption of navelbine was very rapid after oral administration: maximal drug concentrations were reached within the first 1 or 2 h (T_{max}, 0.9–1.75 h; c_{max}, 70.9–832.6 ng/ml), with absorption constants ranging from 0.85 to 2.42 l/h. A comparison of dose-normalised plasma concentration profiles revealed significant time dependence in six evaluable patients (P <0.001). Only four subjects who received low doses ($\leq$100 mg/week) exhibited time-independent kinetics. All of the five patients who were treated at different doses displayed apparent dose dependence (P <0.001). No individual profile was characterised by both time- and dose-independent pharmacokinetics. In all, 18 patients presented biphasic plasma concentration-decay patterns, and only 1 subject exhibited monophasic decay kinetics. The navelbine pharmacokinetic parameters obtained following oral administration were similar to those observed after i.v. bolus injection and were characterised by high oral clearance (0.43–1.45 l h^{-1} kg^{-1}), a large apparent volume of distribution (27.4–45.9 l/kg), and a long terminal half-life (24.2–56.5 h). Large intra- and inter-individual variations in pharmacokinetic parameters were observed. Moreover, after a high dose of 200 mg, an enterohepatic cycle and/or a delay in navelbine's absorption at a distal intestinal site as evidenced by a marked plasma level rebound was observed.

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Introduction

Navelbine (5′-noranhydrovinblastine) is a novel antitumour vinca alkaloid that is semisynthesised by structural modifications on the catharantine moiety of the vinblastine dimer [10, 11]. These modifications render navelbine highly lipophilic. Although it is structurally related to vinblastine and its congeners, this compound is markedly different in its activity, toxicity, and tolerance. Navelbine has demonstrated interesting antitumour properties in experimental systems and a possible lack of cross-resistance with vincristine [12, 13]. In clinical use as a single agent, navelbine is known to be extremely active against non-small-cell lung cancer (NSCLC), advanced breast cancer, and Hodgkin's disease. Its safety and tolerance have been studied in phase I clinical trials involving i.v. doses of up to 43 mg/m^2 [23]. Leucopenia was found to be the main dose-limiting factor; other side effects were mild. No neurotoxicity was observed at doses of <30 mg/m^2 [3]. To date, the clinical pharmacokinetics of navelbine have been investigated following i.v. bolus injections and are characterised by a high systemic clearance (0.27–1.49 l h^{-1} kg^{-1}), a large volume of distribution (8.2–48.2 l/kg), and a long half-life (22.1–67.8 h) [2, 18, 20]. These characteristics of navelbine, together with its high lipophilicity and its binding affinity for tubulin, suggest that continuous exposure to low concentrations can positively affect the drug's activity [1]. However, the latter could easily be achieved by oral administration. Thus, in a first step, tritiated navelbine was given p.o. and i.v. to two patients; the results appeared encouraging, as the bioavailability was about 43% of the delivered dose. However, more data are needed to describe fully the pharmacokinetics of oral navelbine in cancer patients and to address issues such as the relationships between the pharmacokinetic parameters and the toxicity, antitumour activity and spectrum of this drug.

Thus, in an attempt to open a new perspective for the route of delivery of vinca alkaloids, we undertook a pharmacokinetic evaluation of navelbine in 19 cancer patients who received repeated oral doses of the drug. Seven dose levels (from 50 to 200 mg/week) were studied. Navelbine

Table 1. Patients' characteristics and doses

Patient	Sex	Age (years)	Weight (kg)	Diagnosis	Doses (mg/week)[a]	
					First	Second
1	F	56	78	Breast cancer	50 (2)	–
2	M	60	50	Tongue carcinoma	50 (2)	–
3	F	59	75	Breast cancer	50 (2)	–
4	M	39	57	Lymphoma	70 (1)	–
5	M	75	62	Tongue carcinoma	70 (1)	–
6	F	44	61	Breast cancer	70 (1)	180 (1)
7	F	38	59	Breast cancer	100 (1)	–
8	F	58	60	Breast cancer	100 (2)	–
9	F	41	48	Breast cancer	100 (2)	–
10	M	55	70	Lung cancer	130 (2)	200 (1)
11	F	63	50	Breast cancer	130 (2)	180 (1)
12	F	65	48	Breast cancer	130 (1)	–
13	M	23	54	Osteosarcoma	130 (1)	–
14	F	37	55	Breast cancer	160 (1)	180 (1)
15	F	60	60	Breast cancer	160 (1)	–
16	F	37	61	Breast cancer	160 (2)	180 (1)
17	F	59	55	Breast cancer	160 (2)	–
18	F	47	75	Breast cancer	160 (2)	–
19	F	52	60	Breast cancer	160 (1)	–

[a] Number of pharmacokinetically characterised courses are shown in parentheses

plasma concentrations were determined by radioimmunoassay [19]. The aim of the present study was to analyse the effects of time and dose on the kinetic profiles and to estimate the pharmacokinetic parameters of navelbine after oral administration.

Patients and methods

Patients. In all, 14 women presenting with advanced breast cancer and five men exhibiting other histologically documented diseases were entered in the present study (Table 1). Written informed consent was obtained from all patients. Other eligibility criteria included a WHO performance status of ≤ 2, a life expectancy of at least 3 months, an age of 18–80 years, and adequate organ functions as defined by bone marrow (WBC of >3,000/mm^3; granulocyte count of >2,000/mm^3; platelets count of >100,000/mm^3; haemoglobin levels of >10 g/dl), liver (bilirubin, SGOT, SGPT, and alkaline phosphatase <1.25 times the upper limits of normal), and kidney function tests (serum creatinine value of <120 μM/l). No patient had undergone chemotherapy or radiotherapy within 4 weeks of the initiation of navelbine treatment.

Protocol. Navelbine (ditartrate salt; P. F. Médicament, Paris, France) was given orally in capsules using the following dose cascade: 50, 70, 100, 130, 160, 180, and 200 mg/week (Table 1). The patients were fasted overnight and food was reintroduced at 4 h after drug administration. In all, 14 subjects received a single navelbine dose and 5 others were treated with two different doses. For a given dose, each patient underwent four successive treatment courses at 1-week intervals.

Blood samples were drawn at 5 min prior to drug administration and at 15 and 30 min and 1, 2, 4, 6, 12, 24, 36, 48, and/or 72 h after treatment. In general, this sampling schedule was used for only the first and the fourth therapeutic courses, which were then considered to reflect complete pharmacokinetics and were thus considered to be pharmacokinetically evaluable. The number of completely characterised courses for each dose are indicated in Table 1. Blood samples were collected in heparinised glass tubes and immediately cooled at 4° C. The blood was centrifuged at 1000 *g* for 10 min and the resulting plasma was stored frozen at –20° C until analysis.

Table 2. Time and dose dependence of navelbine pharmacokinetics as evaluated by paired comparison of dose-normalised plasma kinetics

Patient	Time dependence (*P*)	Dose dependence (*P*)
1	NS[a]	–
2	NS	–
3	NS	–
6	–	<0.05
8	<0.001[b]	–
9	NS	–
10	<0.001	<0.001
11	<0.001	<0.05
14	<0.001	<0.001
16	<0.001	<0.001
17	<0.001	–
18	<0.001	–

[a] No significant differences between the profiles compared ($P < 0.05$)
[b] Significant differences between the compared profiles that resulted in the rejection of time or dose independence for a given patient
–, Not evaluated

Sample analysis. Plasma navelbine concentrations were measured by radioimmunoassay according to the technique of Rahmani et al. [19]. Briefly, when necessary, plasma was diluted in phosphate-buffered (50 mM; pH 7.4) saline (0.15 M) containing 1 g bovine serum albumin/l (fraction V, Sigma, St. Louis, Mo., USA) and was then incubated at 4° C for 22 h with antiserum and navelbine glycyl-L-tyrosine conjugate tagged with ^{125}I. Human plasma from healthy donors (Centre de Transfusion Sanguine, Marseille, France) was added when needed to maintain a constant amount of human plasma components in the incubation medium. At the end of incubation, polyethylene glycol 6000 (Merck, FRG) was added to obtain a final concentration of 12.5% (w/v). Precipitated immune complexes were separated by centrifugation at 2000 *g* for 10 min and then counted for 1 min on a Kontron MR 252 automatic gamma counter. Navelbine concentrations were determined by interpolation on the logit-log linearised standard curve (useful range, 0.2–25 ng/ml; coefficient of variation <15%). Non-specific inhibitions due to pre-dose plasma binding (always amounting to <10% of control binding) was taken into account in calculations of drug concentrations.

Data analysis. The time (identity of kinetic profiles from one course to another) and dose independence (direct proportionality between the plasma concentration and the dose at any time after administration) of navelbine pharmacokinetics was studied by comparing the dose-normalised plasma concentration profiles. Since the same sampling protocol was used after each dosing phase, the kinetic profiles of a given patient were compared pairwise (the first course was compared with the fourth course for time dependence; the first course at the lower dose was compared with the first course at the higher dose for dose dependence) using a chi-square test [20]. The level of significance was set at $P = 0.05$.

Pharmacokinetic parameters were estimated using a two-compartment linear model that was consistent with the biphasic plasma concentration-decay curves. The three exponential equations describing the model were fitted to the data by a non-linear, weighted least-squares iterative algorithm implemented in an interactive program (APIS) [5, 6]. Absorption followed first-order kinetics and was modelled simultaneously with the other differential equations. The relevant pharmacokinetic parameters (Cl_{oral} and V_{ss}) were computed using the standard equations for fitted parameters. The $t_{1/2}$ value was calculated directly by linear least-squares regression using the terminal-phase data.

Results

The time and dose dependence of navelbine pharmacokinetics following oral administration was assessed by

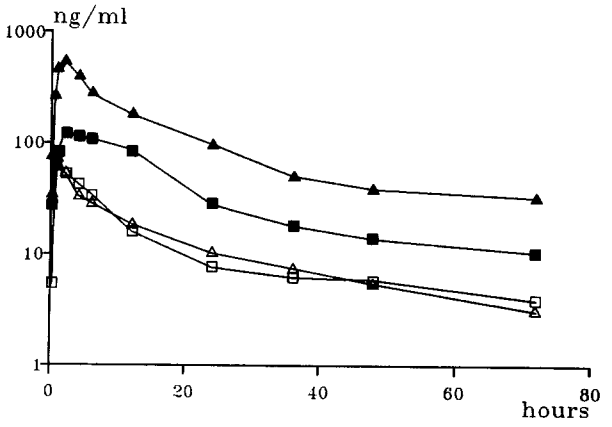

Fig. 1. Time dependence of navelbine pharmacokinetics as analysed by paired comparison of the first course and the fourth course. Both time-independent (patient 1, 50 mg: course 1, □; course 4, △) and time-dependent (patient 17, 160 mg: course 1, ■, course 4, ▲) navelbine plasma kinetics were observed after oral administration

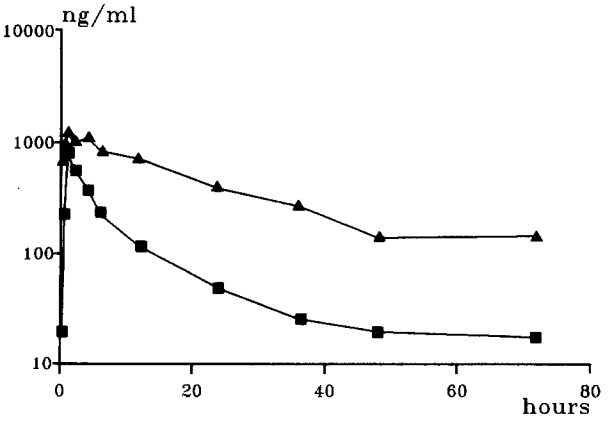

Fig. 2. Dose dependence of navelbine pharmacokinetics as analysed by paired comparison of dose-normalised plasma kinetics (the first course of the lower dose compared with the first course at the high dose). Dose-dependent plasma kinetic profiles (patient 16: 160 mg ■; 180 mg, ▲) were obtained

the paired comparison of dose-normalised plasma concentration-time profiles. The results are shown in Table 2. The time dependence could be evaluated for 10 of the 19 patients (1st course vs 4th course). Only 4 of these 10 subjects exhibited time-independent kinetics at doses of

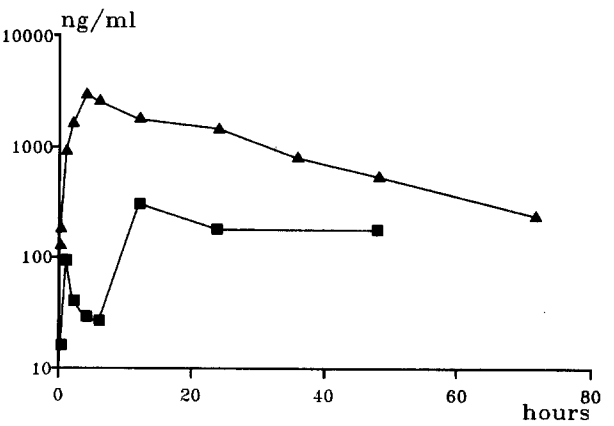

Fig. 3. Two particular navelbine plasma kinetic profiles, including a monophasic plasma decay pattern observed in patient 15 after an oral dose of 160 mg (▲) and a plasma-level rebound noted in patient 10 after a high dose of 200 mg (■)

≤ 100 mg (Fig. 1; 50 mg). For the other 6 patients, kinetic profiles were not superposable and time independence was therefore rejected ($P < 0.001$, Fig. 1; 160 mg). Moreover, time dependence appeared to be more pronounced at high doses (≥ 130 mg, all patients, $P < 0.001$) than at low doses (≤ 100 mg, 4/5 patients, non-significant). The dose dependence was analysed in 5 of the 19 subjects, who received 2 different doses (the 1st course at the lower dose vs the 1st course at the higher dose): all kinetic parameters were apparently dose-dependent (Fig. 2). However, dose dependence could largely be influenced by the time dependence observed in these patients.

After oral administration, navelbine was rapidly absorbed. In most patients, maximal plasma drug concentrations were reached within the first 2 h. The T_{max} and c_{max} values ranged from 0.9 to 1.75 h and from 70.9 to 832.6 ng/ml, respectively; the absorption constant (K_a) ranged from 0.85 to 2.42 l/h. Moreover, the c_{max} value and the weekly doses were significantly correlated ($r = 0.86$; $P < 0.01$). The pharmacokinetic data were well described by a two-compartment model with the exception of those for patient 15, for which a monocompartmental model was used. At a high dose (200 mg), a sharp plasma-level rebound was observed in patient 10 (Fig. 3), making it impossible to fit the data to the pharmacokinetic model. The relevant pharmacokinetic parameters (Cl_{oral} and V_{ss}) and

Table 3. Pharmacokinetic parameters

Dose (mg)	n[a]	T_{max} range[b] (h)	T_{max}[b] (h)	c_{max} (mg/ml)	$t_{1/2}$ (h)	Cl_{oral} (l h^{-1} kg^{-1})	V_{ss} (l/kg)	K_a (l/h)
50	6	0.5–2	0.9	70.9 ± 9.4	30.8 ± 10.5	0.83 ± 0.39	39.9 ± 26.9	2.42 ± 0.97
70	3	1 –2.08	1.28	163.9 ± 105.8	26.1 ± 4.1	1.14 ± 0.7	27.4 ± 13.3	0.93 ± 0.22
100	5	1 –4.08	1.32	170.2 ± 70.3	35.9 ± 8.2	1.37 ± 0.73	45.9 ± 18.2	0.92 ± 0.74
130	6	1 –2	1.05	285 ± 149.6	30.5 ± 6.7	1.45 ± 1.58	35.7 ± 26.3	1.41 ± 0.92
160	9	0.5–4	1.7	832.6 ± 910.4	56.5 ± 37.8	0.43 ± 0.25	34.5 ± 17.7	1.06 ± 0.49
180	4	1 –2.33	1.75	580.5 ± 468.3	24.2 ± 13.2	1.03 ± 0.83	32.8 ± 29.2	0.85 ± 0.39

Data represent mean values ± SD

[a] Number of pharmacokinetically characterised courses for each dose

[b] Harmonic mean and range values for T_{max}

the model-independent parameters (T_{max}, c_{max}, and $t_{1/2}$) are shown in Table 3. Large intra- and inter-individual variations in pharmacokinetic parameters were observed; with time, there was a 17.5% reduction in clearance and a 32.8% increase in half-life for the fourth course as compared with the first course. The pharmacokinetics of oral navelbine was characterised by a high Cl_{oral} value (0.43–1.45 l h^{-1} kg^{-1}), a large V_{ss} value (27.4–45.9 l/kg), and a high $t_{1/2}$ value (24.2–56.5 h). Thus, navelbine's pharmacokinetic parameters after oral administration were essentially the same as those reported following i.v. injection [2, 18, 20].

Discussion

Cancer chemotherapy with antitumour vinca alkaloids has thus far been conducted using i.v. bolus injection and continuous infusion. Only one study has involved the oral administration of vinblastine [4]. Oral forms of these agents have generally not been recommended because of their high toxicities and low tolerated doses. Although oral administration can be very useful in ambulatory treatment, it remained rare for vinca alkaloids until the appearance of navelbine, the most lipophilic of the vinca alkaloids. This drug displays some original and some overlapping antitumour activity as compared with its congeners. Its toxicity is relatively low in patients, and the maximal tolerated dose of navelbine is unexpectedly high. These properties prompted us to give this drug orally to cancer patients in the hope that its oral administration could serve as an alternative to i.v. injection.

The pharmacokinetic behavior of oral navelbine was studied in 19 patients as a part of phase I clinical trials. After oral administration, navelbine was rapidly absorbed. A linear relationship could be established between peak values and weekly doses; however, as the dose increased, the peak occurred more slowly, suggesting the inhibition of drug absorption at high doses. The kinetic profiles were triphasic at doses of <200 mg for 18 patients, involving an initial increasing phase that consisted of the absorption process and the first distribution phase and was followed by two decay phases. These kinetics were well fitted to a two-compartment model using the APIS program. However, for observations made in the same patient, linear modelling implies that kinetics are identical at a constant dose and that plasma concentrations are directly proportional to the dose at any time after administration. One of the aims of the present study was to test these implications. The paired comparison of kinetic profiles obtained after repeated oral administration of the same doses demonstrated significant time dependence in six of the ten evaluable patients. Only four subjects exhibited time-independent kinetics at low doses ($\leq$100 mg). Dose dependence was evaluated in five patients treated at different doses, all of whom exhibited apparent dose-dependent kinetics. However, this dose dependence could have been largely influenced by the time dependence evidenced in these patients.

Navelbine's pharmacokinetic parameters after oral administration were in agreement with those previously reported for i.v. injections [2, 18, 20]. However, as reported for other vinca alkaloids [14], large intra- and interindividual variations in pharmacokinetic parameters were observed. Some authors have suggested that intra- and inter-patient differences in vinca alkaloid pharmacokinetics could be the result of individual differences in hepatic drug disposition and of nonlinear elimination [7, 22] and might be related to the time and dose dependence of these agents [16, 17, 24]. In the present study, we observed a 32.8% increase in half-life and a 17.5% decrease in clearance during the four treatment courses. Such a decrease in clearance has also been reported for vindesine [8, 15–17], vinblastine [9, 21, 25], vincristine [7, 24], and navelbine [20] after i.v. bolus injection and long-term infusion, indicating nonlinear drug elimination. Moreover, a sharp plasma-level rebound was observed during the first or second decay phase in one patient who received 200 mg navelbine. The same phenomenon has also been observed following i.v. injection of the drug [20], suggesting an enterohepatic cycle and/or delayed navelbine absorption at a distal intestinal site. Although these phenomena might occur at low doses, they become more obvious at high doses.

Clinical data demonstrated that oral navelbine was significantly active at least against advanced breast cancer. No unexpected side effects were observed as compared with those observed following i.v. injections. Nausea and vomiting were mild and did not markedly alter drug administration or absorption. However, leucopenia, the dose-limiting toxicity, was found to be correlated with AUC [1].

In conclusion, oral administration of navelbine to cancer patients results in pharmacokinetic characteristics, toxicities, and antitumour activities that are similar to those found following its i.v. injection. Additional bioavailability studies should be carried out in various clinical situations to characterise further the absorption of navelbine and to ensure that its oral administration is both safe and efficacious.

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