Cancer Chemother Pharmacol (1996) 39: 9–16

ORIGINAL ARTICLE

Eric K. Rowinsky · V. Sol Lucas · Ai-Ly Y. Hsieh
William A. Wargin · John A. Hohneker
Barbara Lubejko · Susan E. Sartorius · Ross C. Donehower

The effects of food and divided dosing on the bioavailability of oral vinorelbine

Received: 4 October 1994/Accepted: 15 December 1995

Abstract The effects of food and divided dosing on the bioavailability of a liquid-filled gelatin capsule formulation of vinorelbine (Navelbine), a semisynthetic vinca alkaloid with broad clinical activity, was evaluated in patients with advanced solid tumors. A group of 13 patients were randomized to treatment with the oral formulation at the recommended phase II dose of 80 mg/m^2 per week either in the fasting state or after ingestion of a standard meal. Patients were treated 1 week later in the alternate state relative to their first dose. The effects of divided dosing were assessed during the 3rd week, at which time vinorelbine was administered in two divided doses. After the completion of pharmacokinetic and bioavailability studies, patients received the oral formulation at a dose of 80 mg/m^2 per week in two divided doses to evaluate the feasibility of chronic oral drug administration. Both manipulations resulted in small, albeit statistically significant, reductions in the relative bioavailability of this oral formulation. The relative bioavailability decreased by $22 \pm 28\%$ when treatment followed the ingestion of a standard meal, possibly due to a delay in gastrointestinal transit time. The mean time of maximum plasma concentration (T_{max}) increased from 1.3 ± 1.6 h in the fasting state to 2.5 ± 1.6 h in the fed state, although this difference was not statistically significant. Similarly, the relative bioavailability declined by $16 \pm 51\%$ when vinorelbine was administered in two divided doses. An analysis of dose proportionality revealed disproportionate increases in dose-normalized C_{max} and AUC values with single oral doses above 120 mg, which may account for this phenomenon. The high clearance of vinorelbine, which approaches hepatic blood flow, and the lack of dose proportionality after oral administration, indicate that there is a large first-pass effect which may be saturable, or nonlinear, above single doses of 120 mg. In addition, the toxicological and pharmacological characteristics of oral vinorelbine indicate that treatment after a standard meal or on a divided dosing schedule is safe. Chronic oral administration of the agent in two divided doses was also well tolerated. However, the small reduction in the relative bioavailability following the ingestion of a standard meal and with divided dosing suggest the need for further pharmacodynamic studies to determine if reductions in drug exposure of this magnitude may portend diminished antitumor activity.

Key words Vinorelbine · Navelbine · Oral · Bioavailability · Food · Divided dosing · Pharmacokinetics

E.K. Rowinsky[1] (✉)
Division of Pharmacology and Experimental Therapeutics,
The Johns Hopkins Oncology Center, Room 1–121,
600 North Wolfe Street, Baltimore Maryland 21287–8934
Tel. (410) 955–8902 Fax (410) 550–5499

B. Lubejko · S.E. Sartorius · R.C. Donehower
The Johns Hopkins Oncology Center, Baltimore, Maryland, U.S.A

V.S. Lucas · A.-L.Y. Hsieh · W.A. Wargin · J.A. Hohneker
Burroughs Wellcome Co., Research Triangle Park, North Carolina

Current address
[1] Cancer Therapy and Research Center,
Institute for Drug Development, 8122 Datapoint Drive
San Antonio, TX 78229, USA
Fax: (210) 692-7502

Introduction

Vinorelbine (Navelbine, Burroughs Wellcome Co., Research Triangle, N.C.; 5′-norhydrovinblastine) is the first vinca alkaloid developed since the 1960s that has demonstrated broad clinical antitumor activity. Notable activity has been consistently observed in non-small-cell lung, breast, and ovarian carcinomas, and lymphoma [1–7]. This unique semisynthetic compound differs from other vinca alkaloids in that structural modifications are on the catharanthine ring instead of the vindoline ring [8]. Like other vinca

alkaloids, vinorelbine induces the disassembly of microtubules and the formation of tubulin paracrystals, resulting in the disorganization of the microtubule network [9]. However, the agent may be more specific than other vinca alkaloids in that it preferentially binds to mitotic microtubules and affects axonal microtubules to a lesser degree [10, 11]. In addition, unlike other vinca alkaloids such as vinzolidine, vinleurosine, and vinrosidine which were abandoned early during clinical development due to unpredictable toxic effects [1, 7, 12–14], the principal toxicities of vinorelbine have generally been predictable and manageable [1–7, 15].

To date, no oral vinca alkaloid has reliably demonstrated clinical utility, due to a lack of a feasible oral formulation (e.g. vincristine, vindesine [1]), variable absorption (e.g. vinblastine [12]), or erratic myelosuppression (e.g. vinzolidine [13, 14]). An oral formulation of vinorelbine as a powder-filled capsule was initially developed and later abandoned because the aerosolized drug posed risks to workers during the manufacturing process. Subsequently, a liquid-filled soft gelatin capsule formulation demonstrated acceptable toxicological and pharmacological profiles in a phase I, pharmacologic, and bioavailability study [15]. In this randomized study that evaluated both oral and i.v. dosing in the same subjects, the mean steady-state volume of distribution was large (20.02 ± 8.55 l/kg), the mean harmonic terminal half-life was long (18 h), and the high clearance (CL; mean 0.80 ± 0.68 l/h per kg) approached hepatic blood flow. In addition, bioavailability (F) was low (0.27 ± 12), and absorption was rapid (mean time of maximum plasma concentration, T_{max}, 0.91 ± 0.22 h). These pharmacologic characteristics are indicative of a large first-pass effect. Similar to the i.v. formulation, the principal toxicity of the oral formulation was neutropenia. Nausea, vomiting, and diarrhea were also common but these toxicities were rarely severe and could be ameliorated by using a divided dosing schedule. The study originally evaluated an oral dose of 100 mg/m^2 per week, which resulted in a consistent degree of myelosuppression and in pharmacologic exposures equivalent to the maximally tolerated dose for i.v. administration, 30 mg/m^2 per week. However, the average dose delivered was 82 mg/m^2 due to a high frequency of grade 3 and 4 neutropenia, albeit brief and uncomplicated, and therefore a slightly lower starting dose, 80 mg/m^2 per day, was recommended for subsequent clinical evaluations.

The safe toxicological profile of the liquid-filled soft gelatin capsule formulation, its equivalent pharmacologic profile relative to the i.v. formulation and the many potential advantages of oral drug administration, support a rationale for the further development of the oral formulation. However, moderate interindividual variability in several critical pharmacological parameters, including bioavailability, was also noted in the initial study which was performed under rigorously controlled conditions and close patient supervision during drug administration. Thus, it is likely that interindividual variability may be further accentuated when the oral formulation is used in routine clinical practice where treatment conditions may not be as rigorously controlled and there may be greater variability in patient characteristics that may also affect bioavailability, such as age, gender, liver dysfunction, and relevant genetic polymorphisms [16]. Treatment conditions that may be manipulated in patients receiving oral vinorelbine include the proximity of food ingestion relative to oral drug administration, which is a major contributing factor to individual variation in first-pass metabolism [16], and the use of a divided dosing schedule to ameliorate gastrointestinal toxicity. The principal objectives of this study were to (a) compare the bioavailability of the liquid-filled gelatin capsule formulation of vinorelbine given with and without food, (b) evaluate the effect of divided dosing on key pharmacokinetic parameters and tolerance, and (c) gain additional information regarding the safety of the oral formulation.

Materials and methods

General design

The study was an open label, randomized bioavailability study involving adults with solid tumors conducted at The Johns Hopkins Oncology Center (JHOC), Baltimore, Maryland. Patients were randomized to receive their first dose of oral vinorelbine either in the fasting state or after a standard meal. A second oral dose was given 1 week later in the alternate state relative to the first dose. The third dose was administered in the fasting state but divided into two doses, given 6 h apart. Subsequent doses were given weekly as divided doses 6 h apart. Patients remained on study until disease progression or the severity of toxicity warranted discontinuation. Blood sampling for pharmacokinetic evaluations was performed after the first, second, and third weekly doses to assess the effects of food and divided dosing on drug absorption and bioavailability.

Patient selection

All subjects had histologically documented solid tumors for which no therapies with greater potential benefit than vinorelbine existed. Other pertinent eligibility criteria included: (1) age ≥ 18 years; (2) a Karnofsky performance status $\geq 70\%$ (ambulatory and capable of self-care); (3) a predicted life expectancy ≥ 12 weeks; (4) no major surgery, radiation therapy, or chemotherapy within 21 days of treatment (42 days if the prior chemotherapy regimen included mitomycin-C or a nitrosourea); (5) adequate hematopoietic (absolute neutrophil count [ANC] $> 2000/\mu$l, platelets $> 100\,000/\mu$l, hemoglobin > 9.0 g/dl), hepatic (total bilirubin ≤ 2 mg/dl, AST $< 2.0 \times$ institutional normal upper limit) and renal (creatinine ≤ 2.5 mg/dl) functions; (6) no preexisting clinically significant peripheral neuropathy; (7) no history or evidence of a malabsorption syndrome or disease that may have significantly affected gastrointestinal function; (8) no previous significant surgical resection of the stomach or small bowel; and (9) capacity to ingest a standard meal. All patients gave informed written consent according to federal and institutional guidelines.

Drug administration and dosage

Liquid-filled soft gelatin vinorelbine capsules (40 mg) were formulated by R.P. Scherer (Beinheim, France). The oral dose was calculated to achieve a nominal dose of 80 mg/m^2 during the first 3 weeks of pharmacokinetic sampling. Since the strength of the oral dosage form was fixed, a dosing scheme was constructed to approximate an oral dose of 80 mg/m^2: (1) BSA 1–1.39 m^2, 80 mg (two capsules); (2) BSA 1.4–1.79 m^2, 120 mg (three capsules), and (3) BSA 1.8–2.20 m^2, 160 mg (four capsules). The number of capsules were to be reduced by one for patients with potentially reduced hematopoietic reserves as defined as either previous high-dose therapy with bone marrow rescue, history of poor hematopoietic tolerance to chemotherapy, or previous radiation therapy to more than 25% of marrow-bearing bone. The fasting dose during week 1 or 2 was administered 8 h after eating and 4 h before food ingestion (treatment A). The nonfasting dose during weeks 1 and 2 was administered within 15 min of finishing the standard meal (45 min after starting) (treatment B). The standard meal was a breakfast which was ingested over 30 min and consisted of two eggs, two strips of bacon, toast with butter, 4 oz of hash brown potatoes, 8 oz of whole milk, and water *ad libitum*. After the first two weekly doses, vinorelbine was thereafter given weekly in two divided doses 6 h apart (treatment C). Doses were administered at least 2 h before and 2 h after meals.

Following the first two weekly doses, dose modifications were permitted based on the level of hematologic, neurologic, and/or hepatic toxicity. With respect to dose adjustments for hematologic toxicity, the dose of vinorelbine was reduced by one (BSA 1.0–1.39 m^2) or two (BSA 1.4–2.2 m^2) capsules for ANCs ranging from 1000 to 1499/μl and/or platelet counts ranging from 75 000 to 99 000/μl on the day of treatment. Treatment was delayed for 1 week if the ANC was less than 1000/μl and/or the platelet count was less than 75 000/μl. Dose reductions by one or two capsules were also required for treatment delays ranging from 2 to 3 weeks and/or fever associated with neutropenia irrespective of blood counts on the day of treatment. Patients who required treatment delays in excess of 3 weeks were taken off study. Conversely, escalation of the dose of vinorelbine was allowed by one 40-mg capsule if the patient experienced no neurotoxicity and no more than grade 1 hematological toxicity after 4 consecutive weeks of treatment.

Pretreatment and follow-up studies

A history was taken, and physical examination, and routine laboratory studies were performed and Karnofsky performance status determined at baseline and every 4 weeks. Complete blood counts (CBCs), electrolytes, chemistries, prothrombin and partial thromboplastin times, and urinalysis, were obtained at least weekly before each dose; however, CBCs were performed every other day if the ANC was ≤ 500/μl. Toxicities were graded according to the NCI Common Toxicity Criteria with modification [17]. Formal tumor measurements were performed at baseline and every 8 weeks. A complete response (CR) was scored if there was disappearance of all active disease on two assessments performed at least 4 weeks apart, whereas a partial response required at least a 50% decrease in the sum of the products of the bidimensional measurements of all measurable lesions documented by two assessments separated by at least 4 weeks.

Pharmacokinetic studies

Vinorelbine concentrations in plasma were measured following oral dosing during weeks 1, 2 and 3 (both doses). Venous blood samples were collected into 7-ml tubes containing sodium heparin. Specimens were collected prior to and 15, 30, and 45 min and 1, 1.5, 2, 4, 6, 8, 16, 24, 48, and 72 h after dosing. After immediate centrifugation, plasma samples were transferred to polypropylene tubes and immediately frozen at $-20\,^{\circ}$C until they were analyzed. Plasma samples stored at $-20\,^{\circ}$C were previously demonstrated to be stable for at least 30 weeks [15]. Plasma concentrations were measured by high-performance liquid chromatography (HPLC) as previously described [15].

Natural log-transformed peak area and concentration values of the standards were fitted by a linear regression model. The concentrations of vinorelbine in the unknown samples were calculated by interpolation using the regression line and antilog transformation. The intra-assay precision (expressed as the coefficent of variation, CV) for this assay was previously demonstrated to range from 3% to 5% over the concentration range of 4 to 40 ng/ml [15]. The accuracy (expressed as percentage bias) was within 7% for all concentrations. The interassay precision (6%) and accuracy (7%) were comparable. The lower limit of quantitation for the assay, which was defined as the lowest concentration on the calibration curve with acceptable precision (CV $< 20\%$) and accuracy (bias $< 20\%$), was 2 ng/ml.

Pharmacokinetic analysis

Individual plasma drug disposition curves obtained in the fasting and fed states, as well as with divided dosing, were analyzed by noncompartmental techniques. Maximum plasma concentration (C_{max}) and T_{max} values for oral drug administration were determined by inspection of the plasma disposition curves. Area under the concentration-versus-time curve (AUC) values were calculated using the trapezoidal rule method. Apparent clearance (CL/F) was calculated as,

$$\frac{CL}{F} = \frac{Dose}{AUC}$$

Relative bioavailability of vinorelbine in the fed state (treatment B, F_{rel-b}) or after divided dosing (treatment C, F_{rel-c}) to the fasting state (treatment A) was calculated as,

$$F_{rel-b} = \frac{AUC(B) \times dose(A)}{AUC(A) \times dose(B)}$$

$$F_{rel-c} = \frac{AUC(C) \times dose(A)}{AUC(A) \times dose(C)}$$

Pharmacokinetic values are expressed as means $\pm$ standard deviations. The limit of quantitation of the assay (2 ng/ml) was insufficient to allow a complete description of the terminal phase of disposition, and therefore, plasma half-life and volume of distribution were not calculated.

Results

A group of 13 patients (four males and nine females) with refractory solid tumors received 156 doses of oral vinorelbine. The median age of the patients was 55 years (range 45 to 71 years). One patient (patient 8) who did not complete the required plasma sampling for pharmacokinetic studies due to both toxicity and disease progression was replaced. Primary sites of disease included breast (eight patients), non-small-cell lung (four patients), and unknown primary (one patient). Plasma disposition curves from all three pharmacologic phases of the study in a representative patient are shown in Fig. 1.

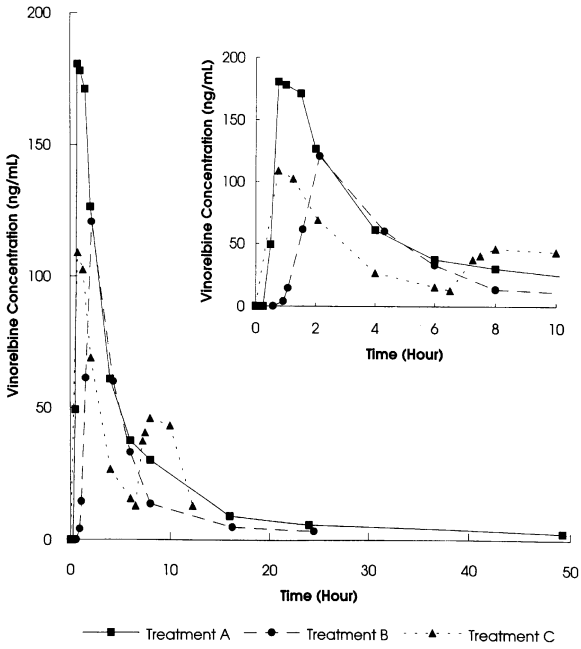

Fig. 1 Plasma disposition curves for patient 5 who received 160 mg vinorelbine in the fasting (treatment A) state, after eating a standard meal (treatment B), and as two divided 80-mg doses (treatment C)

Pharmacologic Studies

Complete plasma sampling was performed in 12 patients in the fasting (treatment A) and fed (treatment B) states and after split dosing (treatment C). One patient (patient 4) was excluded from the analyses due to inappropriate plasma sampling procedures. Seven patients received an oral vinorelbine dose of 120 mg for treatments A, B, and C and four patients were treated with a vinorelbine dose of 160 mg. Relevant pharmacokinetic parameters derived from noncompartmental analysis of plasma concentrations are shown in Table 1. There was significant interindividual variability in AUC, C_{max}, CL/F, and relative bioavailability (F_{rel-b} and F_{rel-c}) values during all three pharmacologic phases of the study.

Food effects

Respective AUC values following treatment with 120 and 160 mg in the fasting state (treatment A) averaged 422 $\pm$ 273 ng/mL h and 604 $\pm$ 214 ng/ml h, whereas AUC values following treatment after a standard meal (treatment B) were 280 $\pm$ 210 ng/mL h and 414 $\pm$ 81 ng/ml-h, respectively. Dose-normalized AUC values were slightly higher for the 160-mg dose than for the 120-mg dose given in the fasting state (3.51 $\pm$ 2.11 ng/ml h and 3.77 $\pm$ 1.16 ng/ml h, respectively) and in the fed state (2.33 $\pm$ 1.62 ng/ml h and 2.58 $\pm$ 0.44 ng/ml h, respectively). Mean C_{max} values following treatment at the 120 and 160 mg dose levels were 71 $\pm$ 30 ng/ml and 144 $\pm$ 48 ng/ml, respectively, in the fasting state and 46 $\pm$ 40 ng/ml (12 to 120 ng/ml) and 90 $\pm$ 30 ng/ml following the standard meal. An analysis of dose-normalized C_{max} values also suggested a lack of dose proportionality at the 120 mg and 160 mg dose levels in both fasting and fed states. Dose-normalized C_{max} values in the fasting state averaged 0.59 $\pm$ 0.28 ng/ml and 0.90 $\pm$ 0.26 ng/ml with the 120 and 160 mg doses, respectively, whereas these dose-normalized values averaged 0.38 $\pm$ 0.31 ng/ml and 0.56 $\pm$ 0.16 ng/ml in the fed state.

Consequently, the administration of oral vinorelbine after a standard meal resulted in reductions in dose-normalized AUC and C_{max} values by 22 $\pm$ 28% (range of reductions 93% to $-$ 7%) and 33 $\pm$ 33% (range of reductions 78% to $-$ 20%), respectively. Paired analysis of both dose-normalized AUC and C_{max} values for individual subjects in the fasting and fed states demonstrated that ingesting a standard meal before treatment significantly affected both parameters (paired *t*-test, two-tailed $P = 0.039$ and $P = 0.0125$, respectively). Consequently, F_{rel-b} averaged 0.77 $\pm$ 0.30. A scatterplot of F_{rel-b} values is shown in Fig. 2. A substantial reduction in bioavailability was noted in only one patient ($F_{rel-b} = 0.07$), whereas F_{rel-b} values for the other ten patients ranged from 0.58 to 1.07. With the exception of patient 6 whose C_{max} was achieved at 6 h post-treatment without any reasonable explanation for the deviation, T_{max} values in the fasting state ranged from 0.5 to 1.5 h, while T_{max} values ranged from 0.5 to 4 h after a standard meal. Although T_{max} values were later when vinorelbine was administered in the fed state in 9 of 11 patients, with mean T_{max} values of 2.5 $\pm$ 1.2 h and 1.3 $\pm$ 1.6 h in the fed and fasting states, respectively, the paired difference in this parameter was not significant (paired *t*-test, two-tailed, $P = 0.09$).

Similar to the results of previous pharmacokinetic studies of vinorelbine [15], apparent oral clearance was high. The large interpatient variability in CL/F values achieved during treatments A and B are displayed in Fig 3. Mean CL/F values were 5.76 $\pm$ 8.05 l/min per m^2 (range, 1.53–26.4 l/min per m^2) following treatment in the fasting state and 8.19 $\pm$ 9.28 l/min per m^2 (2.43–26.0 l/min per m^2) in the fed state.

Divided-dosing

Dividing the dose of vinorelbine into two smaller doses in the fasting state (treatment C) resulted in dose-normalized AUC values that were modestly, albeit significantly, lower than comparable values achieved with single doses (treatment A) (paired *t*-test [two-tailed], $P = 0.03$). Dose-normalized AUC values averaged 3.61 $\pm$ 1.83 ng/ml h and 2.47 $\pm$ 1.41 ng/ml h with single and divided dosing, respectively. Except for patient 3 whose dose-normalized AUC increased 123% with

Table 1 Noncompartmental pharmacokinetic parameters of oral vinorelbine (*treatment A* fasting, *treating B* standard meal, *treatment C* divided dosing)

	AUC (ng/ml h)			C_{max} (ng/m l)				T_{max} (h)				Apparent clearance (CL/F l/min/m^2			Relative bioavailability F_{rel-b}	F_{rtel-c}
Dose (mg)	Treat-ment A	Treat-ment B	Treat-ment C	Treat-ment A	Treat-ment B	Treatment C Dose 1	Dose 2	Treat-ment A	Treat-ment B	Treatment C Dose 1	Dose 2	Treat-ment A	Treat-ment B	Treat-ment C	Treat-ment B/A	Treat-ment C/A
						(80 mg/40 mg)										
120																
Mean	422	280	301	70.6	45.9	48.2	24.5	1.5	2.2	1.6	2.2	7.65	10.9	7.39	0.81	0.95
SD	273	210	202	29.5	39.7	29.4	13.8	2.0	1.3	1.2	0.85	9.81	10.9	8.71	0.36	0.62
CV (%)	65	75	67	41.6	86.4	61.3	56.8	130	59.5	76.1	39.6	128	99.7	118	44.9	64.9
Minimum	48	46	47	16.9	12.2	12.4	3.80	0.50	0.50	0.33	1.5	1.53	2.43	1.77	0.07	0.31
Maximum	750	466	880	107	120	94.0	40.6	6.0	4.0	4.0	4.0	26.4	26.0	26.7	1.07	2.24
						(80 mg/40 mg)										
180																
Mean	804	414	384	144	90	50.5	40.5	0.81	3.0	1.57	1.6	2.44	3.36	5.86	0.71	0.65
SD	214	81	203	47.8	29.7	42.4	20.0	0.24	1.1	1.64	0.48	0.69	0.56	5.96	0.10	0.35
CV (%)	35	20	53	33.2	33	84.0	49.0	29.5	35.8	104.3	29.5	28.3	18.50	102	14.6	53.9
Minimum	439	337	94	75.1	50	17.1	20.0	0.50	2.0	0.50	1.0	1.60	2.77	2.31	0.58	0.19
Maximum	914	539	540	181	121	109	66.2	1.0	4.0	4.0	2.0	3.15	4.10	14.77	0.82	0.94
						(80 mg)										
Harmonic																
Mean						48.9		1.3	2.5	1.6	2.0	5.76	8.19	6.83	0.77	0.84
SD						32.5		1.6	1.2	1.3	0.75	8.05	9.28	7.53	0.29	0.54
CV (%)						67.0		125.0	49.7	81.7	38.6	140	113	110	37.6	63.9
Minimum						12.4		0.5	0.5	0.33	1.0	1.53	2.43	1.77	0.07	0.19
Maximum						109		6.0	4.0	4.0	4.0	26.4	26.0	26.7	1.07	2.24

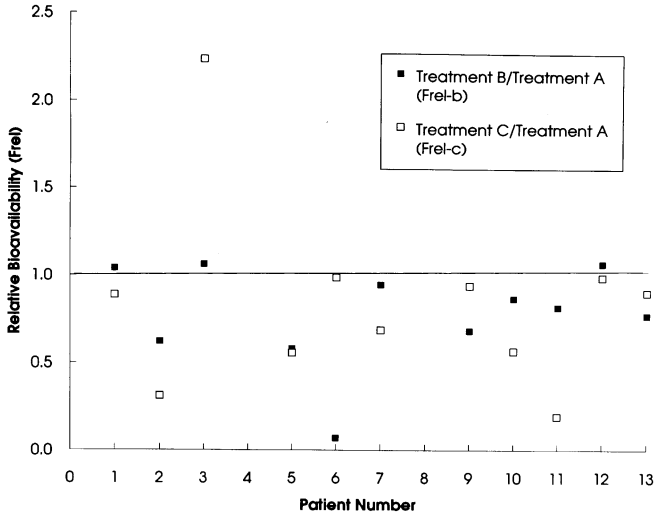

Fig. 2 Relative bioavailability of vinorelbine following the ingestion of a standard meal (treatment B) and with divided dosing (treatment C) relative to fasting (treatment A) in individual patients

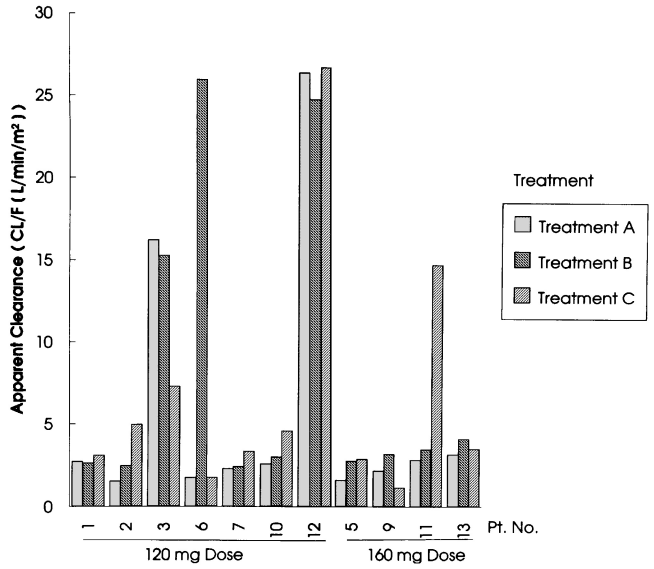

Fig. 3 Apparent clearance in individual patients following fasting (treatment A), the ingestion of a standard meal (treatment B), and divided dosing (treatment C)

divided dosing, dose-normalized values in the other ten patients decreased by 1% to 81% (mean 30.5%) with divided dosing. Consequently, F_{rel-c} averaged 0.84 $\pm$ 0.54, indicating a modest decrease in the relative bioavailability with divided dosing. Divided dosing was associated with F_{rel-c} values above 1 in one patient (2.24), whereas F_{rel-c} values less than 1 (range, 0.19–0.99) were noted in the remaining ten patients as shown in the scatterplot of F_{rel-b} values in Fig. 2. Dose-normalized C_{max} values achieved after single doses of 40, 80, and 120 mg in the fasting state were similar, averaging 0.62 $\pm$ 0.32 ng/ml, 0.58 $\pm$ 0.35 ng/ml, and 0.59 $\pm$ 0.23 ng/ml, respectively, indicating proportionality within this dosing range. However, the dose-normalized C_{max} at the 160-mg dose in the fasting state was much higher, 0.90 $\pm$ 0.26 ng/ml, which suggests a lack of dose-proportional behavior with single oral doses above 120 mg, although the sample size at the 160-mg dose level was small ($n = 4$). A similar analysis of dose proportionality using dose-normalized AUC values was not performed because the proportion of the total AUC that was contributed by each of the two smaller split doses (40 and 80 mg) could not be estimated reliably using noncompartmental methods. There was large interpatient variability in T_{max} values but there was no indication of a significant difference in this parameter between single- and split-dosing schedules. Large interpatient differences in CL/F values were also observed with the split-dosing schedule. Mean CL/F values were 5.76 $\pm$ 8.05 l/min per m^2 and 6.83 $\pm$ 7.53 l/min per m^2 on single- and split-dosing schedules (treatments A and C), respectively.

Toxicities

The nature of the toxicities noted with oral vinorelbine was similar to those described in a previous bioavailability study of the identical oral formulation but there was a much lower rate of toxic effects, possibly reflecting the use of a lower nominal dose (80 mg/m^2) in this study compared to the previous trial (100 mg/m^2). The major toxicity was leukopenia, principally neutropenia; however, only one patient experienced grade 3 neutropenia. Grade 1 nausea and vomiting was observed in nine patients and grade 1 diarrhea was noted in seven patients. Three patients also experienced grade 1 paresthesias. A 71-year-old patient (patient 8) with extensive prior radiation therapy to the head and neck, experienced severe mucositis and neutropenia after her first and only dose. Therapy was discontinued due to progressive disease and severe stomatitis.

Activity

One major response was noted during the study. A CR was documented in a 59-year-old female with metastatic breast cancer involving her lungs that had previously responded to a combination chemotherapy regimen containing doxorubicin. The CR was confirmed after 5 months of therapy with vinorelbine and the patient declined further treatment after 7 months on continuous treatment. Follow-up computerized tomographic scans showed small pulmonary nodules 22 months after beginning therapy. At 27 months, the patient was asymptomatic and opted not to restart cytotoxic chemotherapy at that juncture.

Discussion

An oral formulation of vinorelbine may have several advantages, particularly with regard to patient convenience, lower drug administration costs, and the increased feasibility of developing alternate treatment schedules such as chronic low-dose administration. However, oral anticancer drugs may also be disadvantageous, especially with respect to the potential for significant interindividual variability in gastrointestinal absorption and bioavailability [16, 18]. For the liquid-filled gelatin capsule formulation of vinorelbine, interindividual variability in several relevant pharmacologic and absorption parameters is large, albeit similar to other commonly used oral drugs such as etoposide, cyclophosphamide, and hexamethylmelamine [19–23]. For example, although mean absolute bioavailability in 16 patients treated with two oral doses of vinorelbine in the fasting state under identical conditions was similar ($27 \pm 14\%$ and $25 \pm 11\%$) intraindividual CV values averaged 32%. It is possible that this magnitude of variability may be further accentuated by the higher level of variability in patient characteristics and day-to-day treatment conditions that occurs with routine outpatient drug administration [16].

This study demonstrated that two common treatment condition variables that may be manipulated during routine outpatient treatment with vinorelbine, such as the proximity of food ingestion relative to drug administration and the use of a divided dosing schedule, significantly affects the bioavailability of the liquid-filled gelatin capsule formulation. Nevertheless, the magnitude of these effects was small. The ingestion of a standard meal before treatment resulted in a $22 \pm 28\%$ reduction in relative bioavailability, with only 1 of 11 patients (8.3%) experiencing a substantial ($> 50\%$) change as shown in Fig. 2. Although the explanation for this observation is not entirely clear, it is possible that the ingestion of a standard meal increases the gastrointestinal transit time for the oral formulation. This is suggested by longer T_{max} values when treatment followed the ingestion of a standard meal (2.5 ± 1.2 h) compared to treatment in the fasting state (1.3 ± 1.6 h). In addition, T_{max} values were longer in 10 of 11 patients when oral vinorelbine was administered after a standard meal. Although a paired analysis failed to show a significant difference in T_{max} values between fasting and fed states, this parameter is often subject to significant variability, depending, in part, on the frequency and timing of plasma sampling. Thus, statistically significant differences in T_{max} may not be evident unless the magnitude of the effects of a standard meal on gastrointestinal transit time and bioavailability are very large.

The bioavailability of several other oral drugs has been also shown to be significantly reduced when they are administered with food. Such has been demonstrated for hydralazine where potential explanations have ranged from reductions in drug absorption or drug binding, and/or increased drug metabolism during feeding [24, 25]. Hydralazine's first-pass behavior appears to be nonlinear, and transient increases in hepatic blood flow may reduce drug concentrations in the portal vein during feeding, which may change the first pass metabolism from nonlinear to linear. In contrast, in most situations where food significantly affects the bioavailability of oral drugs subject to first-pass effects, bioavailability is generally increased [16]. Although it was originally felt that these alterations were due to substantial increases in hepatic blood flow or protein binding postprandially, these possibilities have been shown to play only a minor role, if any [16]. Instead, recent studies suggest that food transiently reduces the intrinsic ability of the liver to metabolize highly extracted drugs, particularly during the absorption phase. However, food does not affect the bioavailability of a large number of highly extracted drugs, particularly lipophilic compounds [16].

Similarly, administering vinorelbine on a divided dosing schedule, which has been reported to result in decreased gastrointestinal toxicity [15], was associated with a modest, albeit statistically significant, reduction in relative bioavailability. One possible explanation for this observation is evident from the analysis of dose proportionality achieved with single doses of 40, 80, 120, and 160 mg. C_{max} values normalized for dose were similar at doses ranging from 40 to 120 mg; however, a disproportionate increase in the dose-normalized C_{max} value was noted at the 160-mg dose level. Similarly, an analysis of dose-normalized AUC values revealed a lack of dose proportionality between the 120-mg and 160-mg dose levels. Thus, nonlinear increases in C_{max} and AUC values, and hence bioavailability, with higher single doses may account for the modest reduction in the relative bioavailabilty of vinorelbine when administered on a divided dosing schedule. A nonlinear or saturable first-pass effect may account for the reductions in both AUCs and bioavailability with the divided dosing schedule and the lack of clear dose proportionality as single doses are increased above 120 mg. The fraction of drug that is extracted by the liver, or intestinal wall, during the first-pass has also been demonstrated to increase with dose for several other drugs with high hepatic extraction ratios, including 5-fluorouracil, hydralazine, lorcainide, propranolol, and phenacetin [26]. Since oral vinorelbine's clearance is high, approaching hepatic blood flow, indicating a large first-pass effect, even a negligible degree of nonlinear, or saturable, first-pass clearance may result in a significant increase in bioavailability when threshold concentrations in the portal circulation are exceeded. Unlike the aforementioned drugs that undergo significant hepatic metabolism during first-pass, the explanation for the high extraction and seemingly high first-pass effect clearance of oral vinorelbine is not

entirely clear. To date, large quantities of metabolites have not been found in urine, feces or plasma. Instead, hepatic clearance and subsequent biliary excretion of the parent compound may account for a substantial proportion of total drug disposition since significant quantities of the unmetabolized drug have been recovered from the bile of animals [27].

Based on the toxicological and pharmacological results of this study, vinorelbine may be administered safely as a liquid-filled, gelatin capsule after a standard meal and on a divided dosing schedule at the recommended phase II dose of 80 mg/m^2 per week. However, the small, albeit significant, reductions in bioavailability that occur with both measures may result in decreased antitumor activity, especially if antitumor activity is truly related to drug exposure. Therefore, phase II studies of the oral formulation should incorporate the means for dose modifications to achieve a specified level of hematological effects, as well as ancillary population pharmacokinetic studies to determine whether such pharmacodynamic relationships exist, particularly if the achievement of a critical AUC value or maintenance of a threshold concentration for a specific time are necessary for antitumor activity. The existence of such information may either reduce or heighten the concern about modifications in drug administration conditions and scheduling that may occur during routine outpatient treatment, such as the interchangeability of single and divided dosing schedules and drug treatment relative to the ingestion of food.

Acknowledgements The author wish to thank Mary Duerr for assistance with study coordination and data collection, and patient care; T-L. Chen, Lisa Hurowitz and Shirley George for assistance with sample processing; and the referring medical staff, and medical and nursing staffs of The Johns Hopkins Oncology Center for the care of the patients in this study. The study was supported by a grant from Burroughs Wellcome Co., Research Triangle Park, North Carolina.

References

1. Rowinsky EK, Donehower RC (1991) The clinical pharmacology and use of antimicrotubule agents in cancer chemotherapeutics. Pharmacol Ther 52:35–84
2. Armand JP, Marty M (1989) Navelbine: a new step in cancer therapy. Semin Oncol 16 [Suppl 4]:41–45
3. Sorensen JB (1992) Vinorelbine. A review of its antitumour activity in lung cancer. Drugs 44 [Suppl 4]:60–65
4. Cvitkovic E, Izzo J (1992) The current and future place of vinorelbine in cancer therapy. Drugs 44 [Suppl 4]:36–45
5. Marty M, Extra JM, Dieras V, Giacchetti S, Ohana S, Espie M (1992) A review of the antitumour activity of vinorelbine in breast cancer. Drugs 44 [Suppl 4]:29–35
6. Spielmann M, Dorval T, Turpin F, Antoine E, Jouve M, Maylevin F, Lacombe D, Rouesse J, Pouillart P, Tursz T, Merle, S (1994) Phase II trial of vinorelbine/doxorubicin as first-line therapy of advanced breast cancer. J Clin Oncol 12:1764–1770
7. Budman DR (1992) New vinca alkaloids and related compounds. Semin Oncol 19:639–645
8. Potier P (1989) The synthesis of Navelbine prototype of a new series of vinblastine derivatives. Semin Oncol 16 [Suppl 4]:2–4
9. Fellous A, Ohayon R, Vacassin T, Binet S, Lataste H, Krikorian A, Couzinier JP, Meninger V (1989) Biochemical effects of Navelbine on tubulin and associated proteins. Semin Oncol 16 [Suppl. 4]:9–14
10. Binet S, Fellous A, Lataste H, Krikorian A, Couzinier JP, Meninger V (1989) In situ analysis of the action of Navelbine on various types of microtubules using immunofluorescence. Semin Oncol 16 [Suppl 4]:5–8
11. Binet S, Chaineau E, Fellous A, Krikorian A, Couzinier JP, Meninger V (1990) Immunoflourescence study of the action of Navelbine, vincristine, and vinblastine on mitotic and axonal microtubules. Int J Cancer 46:262–266
12. Hodes M, Rohn R, Bond W, Corpening WG, Yardley JM, (1961) Vincaleukoblastine III. Clinical trial with the oral preparation. Cancer Chemother Rep 14:129
13. Kreis W, Budman D, Schulman P, Freeman J, Griest A, Nelson RL, Marks M, Kevill L (1986) Clinical pharmacology of vinzolidine. Cancer Chemother Pharmacol 16:70–74
14. Taylor C, Salmon S, Satterlee W, et al (1990) A phase I and pharmacokinetic study of intravenous vinzolodine. Invest New Drugs 8:551–557
15. Rowinsky EK, Noe DA, Lucas VS, Winer E, Lucas VS, Wargin WA, Hohneker J, Lubejko B, Sartorius JE, Ettinger DJ, Douhower RC (1994) A phase I, pharmacokinetic and absolute bioavailability study of oral vinorelbine (Navelbine) in solid tumor patients. J Clin Oncol 12:1754–1763
16. Tam YK (1993) Individual variation in first-pass metabolism. Clin Pharmacokinet 25:300–325
17. National Cancer Institute (1988) Guidelines for reporting of adverse drug reactions. Division of Cancer Treatment, National Cancer Institute, Bethesda
18. Pinedo HM (1994) Vinorelbine: a horse of a different color? J Clin Oncol 12:1745–1747
19. D'Incalci MD, Bolis G, Mangoini C, Morasca L, Garattini S (1978) Variable oral absorption of hexamethylmelamine in man. Cancer Treat Rep 62:173–175
20. Smyth R, Pfeffer M, Scalzo A, Comis RL (1985) Bioavailability and pharmacokinetics of etoposide (VP-16). Semin Oncol 12:48–51
21. Hande KR, Krozely MG, Greco A, Hainsworth JO, Johnson DH (1993) Bioavailability of low-dose etoposide. J Clin Oncol 11:374–377
22. Wagner T, Fenneberg K (1984) Pharmacokinetics and bioavailability of cyclophosphamide from oral formulations Arzneimittelforschung 34:313–314
23. Juma FD, Rogers HJ, Trounce JR (1979) Pharmacokinetics of cyclophosphamide and alkylating activity in man after intravenous and oral administration. Br J Clin Pharmacol 8:209–217
24. Shepherd AMM, Irvine NA, Ludden TM (1984) Effect of food on blood hydralazine levels and response in hypertension. Clin Pharmacol Ther 36:14–18
25. Semple HA, Koo W, Tam YK, Ngo LY, Coutts RT (1991) Interactions between hydralazine and oral nutrients in humans. Ther Drug Monit 13:304–308
26. Rowland M, Tozer TN (1989) Clinical pharmacokinetics, 2nd edn. Lea and Febiger, Philadelphia, pp 392–393
27. Leveque D, Merle-Melet M, Bresler L, Didelot JP, Aymard JP, Wihlm J, Jenl F (1993) Biliary elimination and pharmacokinetics of vinorelbine in micropigs. Cancer Chemother Pharmacol 32:486–490