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Pharmacokinetics of vindesine bolus and infusion

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Summary. *The pharmacokinetics of vindesine were investigated during treatment of 15 patients with progressive malignancies refractory to conventional treatment. Patients were administered one of three IV dose schedules: 3.0 mg/m² bolus injection, 1.2 mg/m²/day infusion for 5 days, or 2.0 mg/m²/day infusion for 2 days. Concentrations of the drug in the serum and urine were determined by radioimmunoassay. Serum concentrations were highest (5×10^{-7} M) in patients receiving a bolus injection, but fell to nondetectable levels by 48 h in four of five patients (terminal $t_{1/2}$ 15.0 ± 9.4 h). Compared with bolus injection, 1.2- to 1.4-fold greater areas under the blood concentration curve were observed during infusions of 2.0 mg/m² and 1.2 mg/m². Whereas steady-state concentrations (~ 1×10^{-8} M) were maintained throughout the infusion of 1.2 mg/m²/day progressively increasing serum levels were observed during the infusion of 2.0 mg/m²/day. Serum concentrations fell rapidly following discontinuation of the 2.0-mg/m² infusion, but were somewhat more sustained in the 1.2-mg/m² infusion group. The average urinary excretion was similar for each dose-schedule (8%–11% of the total dose). The pharmacokinetics of vindesine are influenced by variations in dose schedule.*

Introduction

Vindesine (desacetyl vinblastine carboxyamide), a new semisynthetic derivative of vinblastine, has been tested in numerous phase-I and -II trials using IV bolus injection [3, 6, 8]. Recently, infusion of this agent [1, 2, 4, 16, 22] and the other clinically useful vinca alkaloids, vinblastine [21] and vincristine [10], has been investigated. Bayssas et al. [1] have demonstrated the ability of continuous IV infusions (2.0 mg/m² on 2 consecutive days) to induce remissions in lymphomas and acute leukemia after failure of bolus injection of vindesine. Similarly Bodey et al. [2] have obtained partial remissions in patients with advanced breast cancer following 5-day continuous IV infusions (1.2–1.4 mg/m²/day) after failure of vindesine given by bolus injection.

The current investigation was undertaken to explore the pharmacology of vindesine when given by IV bolus injection and continuous IV infusion. Such pharmacokinetic data might prove to be useful for the design of future clinical trials of this promising antitumor agent.

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Materials and methods

Subjects. Between March 1981 and October 1981, a group of 15 consecutive patients with histologically confirmed malignancy refractory to conventional therapy received vindesine; samples of blood and urine were obtained following informed consent. Patient characteristics are given in Table 1. Two patients (FV and FH) received both a bolus injection and an infusion of vindesine. Eligibility requirements included a white blood cell count of ≥ 4,000/mm³ and platelet count ≥ 100,000/mm³ (unless myelosuppression was secondary to the underlying malignancy), blood urea nitrogen ≤ 25 mg% and serum creatinine ≤ 1.5 mg%, serum bilirubin ≤ 1.0 mg% and SGOT ≤ 40 IU, and absence of neurologic disorders.

Treatment design. Patients were treated according to one of three dose-schedules for vindesine (Eli Lilly and Co., Indianapolis, Ind). Five patients received an IV bolus injection of 3.0 mg/m² over 1–3 min; a continuous IV infusion of 1.2 mg/m² daily for 5 days was given to six patients; and six patients received a continuous IV infusion of 2.0 mg/m² daily for 2 days. Infusion solutions consisted of 1,000 ml 5% dextrose in water, to which was added the appropriate daily dose of vindesine; 3,000 U of heparin and 50 mg hydrocortisone were added to the infusate to reduce phlebitis. No cytotoxic agents other than vindesine were administered during this investigation, but supportive medications such as narcotics, antiemetics, stool softeners, etc. were used when necessary.

Samples. Serial serum samples during treatment or after infusion were obtained by removal of 3 ml whole blood from the arm opposite the injection or in the same arm below the site of administration. A 23-gauge scalp vein needle was attached to a heparin lock (Abbott Co., Chicago, Ill), from which multiple blood samples were removed during the first 12–24 h following vindesine administration; venipuncture was used to obtain samples at later time points. Blood samples were centrifuged and the resultant sera were stored at −20° C until processed. Sample time points included the following: 0 (prior to injection), 5, 10, 15, 20, 30, 60 min, 2, 3, 4, 6, 8, 12 h, and daily.

Urine samples consisted of the total daily voided urine, which was collected in containers cooled with ice. After the daily volume had been recorded an aliquot was stored at −20° C until processed.

Table 1. Patient characteristics

Dose schedule	Patient	Age (years)	Sex	Body surface area (m^2)	Primary cancer
3.0 mg/m^2 bolus	FV	61	F	1.78	Lung
	GS	55	F	1.83	Breast
	EG	46	F	1.58	Lung
	AN	62	M	1.60	Lung
	FH	38	F	1.72	Breast
1.2 mg/m^2/day infusion × 5 days	FV	61	F	1.78	Lung
	FH	38	F	1.72	Breast
	RW	32	M	2.00	Colon
	SM	77	F	1.70	Endometrium
	RH	56	M	2.00	Acute leukemia
	LM	50	F	1.40	Acute leukemia
2.0 mg/m^2/day infusion × 2 days	NB	64	F	1.42	Breast
	LC	34	F	1.64	Colon
	MH	57	F	1.60	Breast
	LL	52	F	1.56	Breast
	MG	43	F	1.60	Breast
	WD	58	M	1.88	Multiple myeloma

Assay. Vindesine concentrations in the serum and urine samples were determined by a radioimmunoassay with a sensitivity to $\sim 10^{-9}$ *M* [19]. The reference sample was obtained from Eli Lilly and Co., Indianapolis, Ind; it gave a single spot by thin-layer chromatography on silica gel plates in diethyl ether : *N*-propyl alcohol : triethylamine (24 : 16 : 2, by vol) and chloroform : methanol : formic acid (70 : 20 : 5, by vol) solvent systems. Tritium-labeled vinblastine (specific activity, 10.4 Ci/mmol) was purchased from Amersham/Searle Corp., Arlington Heights, Ill. The unfractionated lyophilized antiserum, obtained from rabbits by injection of 4-deacetylvinblastine C-3 carboxazide coupled to bovine serum albumin, was kindly provided by Dr Mary Root, Lilly Research Laboratories, Indianapolis, Ind. Appropriate dilutions of the serum or urine samples were made in the glycine buffer [0.2 *M* glycine-HCl, pH 8.8; 0.25% crystalline human albumin (ICN Pharmaceuticals, Inc., Cleveland, OH); 1% normal lamb serum (North American Biologicals, Inc., Miami, Fla); and 242 mg Merthiolate/l. In duplicate glass test tubes, 50 µl diluted antiserum and 50 µl glycine buffer were incubated for 60 min at 4° C in enclosed plastic containers, after which 50 µl 1 : 2,400-diluted ^{3}H-vinblastine in the glycine buffer was added to each tube. The reaction mixtures were allowed to incubate for another 60 min in the refrigerator. At the end of the incubation period, 200 µl well-stirred dextran-coated charcoal suspension [1% carbon decolorizing (Fisher Scientific Co., Fairlawn, NJ) and 0.5% dextran 70 (Pharmacia Fine Chemicals, Co., Uppsala, Sweden) suspended in the glycine buffer] was added to each tube, and the contents were mixed thoroughly, kept at room temperature for 20 min, and centrifuged at 2,700 rpm for 10 min. Two hundred and fifty microliters of the clear supernatant from each tube was mixed thoroughly with 4 ml toluene-PPO-POPOP: Triton X-100 (2 : 1) scintillation fluid, and the radioactivity was counted against an external standard in a liquid scintillation counter. Radioactivity from each sample was converted into dpm from a standard quench curve. The total amount of input radioactivity was used as the basis for calculation of the percent labeled alkaloid bound, after subtraction of the nonspecific radioactivity. The nonspecific binding of the ^{3}H-vinblastine was between 1% and 3% of the total input radioactivity. For these calculations a computer program was designed, which converted the raw cpm data into dpm, took an average of the duplicate values, subtracted the background, and calculated the percent bound radioactivity. From the known amount of vindesine and percent bound radioactivity, a standard curve for each experiment was plotted on a log-logit graph, from which the amount of vindesine present in each diluted serum or urine sample was determined. Fifty percent competition levels of vindesine in the assay were in the range of 0.5–0.7 ng. Vindesine concentrations closest to 50% competition of binding were taken as final values. The results were expressed as concentrations of vindesine which refer to vindesine equivalents (parent drug and its metabolic and/or decomposition products detected by the radioimmunoassay).

Data analysis. Inspection of the drug concentration-time data plotted on semilogarithmic paper revealed a triexponential decay pattern following IV bolus injection. Initial pharmacokinetic parameter estimates were obtained using a modified CSTRIP program [18] to yield the apparent volume of the central compartment (Vc) along with the microscopic rate constants. These data were further analyzed through the use of a nonlinear least-square regression program NONLIN [13] in conjunction with a specific subroutine for a three-compartment open model. The triexponential decay can thus be expressed by Eq. (1):

$$C_1 = A_1 e^{-\alpha t} + A_2 e^{-\beta t} + A_3 e^{-\gamma t}, \quad (1)$$

where C_1 is the serum drug concentration at time *t;* A_1, A_2, and A_3 are the intercepts on the ordinate at time zero; and α, β, and γ are the first-order disposition rate constants. A weighting function of $1/C_1$ was used in the NONLIN analysis. There are several possible three-compartment open models for IV bolus injection [20]. In this paper we have used a model in which the drug is injected into the central compartment 1, from which the elimination also takes place. The microscopic rate constants (k_{10}, k_{12}, k_{21}, k_{13} and k_{31}) in the model were calculated by the NONLIN computer program [13]. The half-life for each phase

was calculated from the equation: $t_{1/2}$ = 0.693/rate constant. The area under the serum concentration-time curve from time zero to infinity (AUC_0^∞) was determined by Eq. (2):

$$AUC\ \infty = \frac{A_1}{\alpha} + \frac{A_2}{\beta} + \frac{A_3}{\gamma}. \quad (2)$$

Apparent volume of the central compartment (V_c) was calculated by Eq. (3):

$$V_c = \text{Dose}/A_1 + A_2 + A_3\,. \quad (3)$$

The apparent volume of distribution, V_D, was calculated by Eq. (4):

$$V_D = \frac{\text{Dose}}{AUC_0^\infty \times \text{terminal rate constant}}\,. \quad (4)$$

The plasma clearance was calculated by Eq. (5):

$$\text{Plasma clearance} = \frac{\text{Dose}}{AUC_0^\infty} \quad (5)$$

Postinfusion pharmacokinetic data were also analyzed with the aid of CSTRIP and NONLIN programs, and these data gave a best fit for a biexponential decay model:

$$C_1 = A\,e^{-\alpha t} + B\,e^{-\beta t}\,.$$

The volume of distribution, V_D was calculated by Eq. (6):

$$V_\beta = \frac{k_0}{\beta \cdot Css}, \quad (6)$$

where k_0 was the rate of infusion and *Css* in the steady-state vindesine concentration.

The area under the drug concentration-time curve (AUC) in patients undergoing infusion treatment was determined by trapezoidal method [20].

Results

The serum concentrations of vindesine attained during each of the dose schedules are depicted in Fig. 1. Whereas the peak serum concentration ($\sim 5 \times 10^{-7}\,M$) occurred after 5 min following a 3.0-mg/m^2 IV bolus injection, the maximum serum concentration during the daily infusion of 2.0 mg/m^2 ($\sim 5 \times 10^{-8}\,M$) occurred at 48 h, which was at the completion of the infusion. Unlike the progressively increasing levels observed after the 24-h time point for the 2.0-mg/m^2 infusion, the serum concentrations appeared to reach steady-state conditions at 12–24 h following initiation of the 1.2-mg/m^2 infusion, and remained $\sim 1 \times 10^{-8}\,M$ throughout the infusion. Serum concentrations remained in the undetectable range of the radioimmunoassay for the majority of patients during the first 10–15 min of the 2.0-mg/m^2 infusion and 4–6 h of the 1.2-mg/m^2 infusion. The blood concentration curves appeared to converge to a level of $\sim 1 \times 10^{-8}$ at 24 h after initiation of each of the dose schedules and remained at or above this concentration during the remainder of the infusions. However, by 48 h after the bolus injection of 3.0 mg/m^2, only one of five patients had detectable serum concentrations of vindesine.

The pharmacokinetic parameters of vindesine bolus injection are given in Table 2. The blood decay curve following bolus injection was triexponential, with mean half-lives of 0.04 ± 0.02, 0.42 ± 0.17, and 14.97 ± 9.44 h. Avid tissue binding by vindesine was suggested by the finding of the lowest microscopic rate constant between the tissue compartment and central compartment (k_{31} = 0.0064 ± 0.0020/min) compared with the other microscopic rate constants (k_{10} = 0.1283 ± 0.0625; k_{12} = 0.1589 ± 0.0550; k_{21} = 0.0865 ± 0.0325; and k_{13} = 0.1932 ± 0.0642/min). The average apparent volume of the central compartment approximated plasma volume. The mean volume of distribution was 117 l/m^2 surface area, which exceeded total body water.

The average areas under the blood concentration curve (AUC), uncorrected for total dosage, were 1.2- to 1.4-fold greater during infusions than those observed following bolus injection (Table 3). Despite a greater mean total dose of vindesine administered during 1.2-mg/m^2 infusions (10.6 ± 0.5 mg) than with 2.0-mg/m^2 infusions (6.4 ± 0.3 mg), the average values of AUC with the two infusion dose schedules were very similar (76,525 and 70,866 mM × min, respectively). This was associated with a somewhat greater AUC inscribed per milligram of administered vindesine during infusions of 2.0 mg/m^2 (10.735 nM × min) than during 1.2-mg/m^2 infusions (7,262 nM × min) and a correspondingly lower plasma clearance rate (161 and 222 ml/min, respectively).

Postinfusion serum samples were obtained in five of six patients who received 1.2-mg/m^2 infusions; and adequate number of data points allowed pharmacokinetic analysis in three patients (Table 4). In the other two patients in this group (FH and SM) serum concentrations of vindesine fell rapidly after discontinuation of the infusion, which might have been due to the presence of large volumes of extravascular fluid. In one patient (FH), in whom a large pleural effusion was present, serum levels were undetectable at the completion of infusion. In the other patient, SM, blood concentrations were

Table 2. Pharmacokinetic parameters of vindesine bolus injection

Dose/m^2 (mg)	Patient	Serum half-lives (h)			Volumes (l/m^2 surface area)[a]	
		α	β	γ	V_C (Central)	V_β (Distant)
3.0 (5.3)	FV	0.10	0.96	4.83	5.08	76.60
3.0 (5.5)	GS	0.04	0.64	8.83	1.95	96.35
3.0 (4.8)	EG	0.03	0.26	7.27	1.22	76.70
3.0 (4.8)	AN	0.01	0.13	1.52	3.79	157.60
3.0 (5.0)	FH	0.02	0.10	52.42	0.89	176.80
	$\bar{x}$ ± SEM	0.04 ± 0.2	0.40 ± 0.20	15.97 ± 9.44	2.59 ± 0.80	116.81 ± 21.10

[a] Normalized to 1.73 m^2 surface area

Table 3. Pharmacokinetic parameters of vindesine bolus and infusion

Dose schedule	Patient	Dose (mg)	AUC[a] (nM × min)	AUC (nM × min)/mg	Plasma clearance (ml/min/m^2)[b]
3.0 mg/m^2 bolus	FV	5.3	33,048	6,188	182.9
	GS	5.5	48,049	8,752	125.8
	EG	4.8	50,215	10,461	121.9
	AN	4.8	12,336	2,570	490.1
	FH	5.0	140,332	28,066	41.5
	$\bar{x}$	5.1	56,796	11,207	192.4
	(SEM)	(± 0.1)	(± 21,953)	(± 4,419)	(± 77.8)
1.2 mg/m^2/day infusion × 5 days	FV	10.5	75,947	7,233	157.7
	FH	10.5	78,599	7,481	157.8
	RW	12.0	24,551	2,045	496.2
	SM	10.0	40,981	4,098	291.4
	RH	12.0	157,770	13,147	77.2
	LM	8.5	81,340	9,569	151.5
	$\bar{x}$	10.6	76,525	7,262	222.0
	(SEM)	(± 0.5)	(± 18,791)	(± 1,605)	(± 61.7)
2.0 mg/m^2/day infusion × 2 days	NB	5.4	45,457	8,418	169.8
	LC	6.4	130,688	16,201	76.4
	MH	6.4	45,342	7,084	179.1
	LL	6.2	23,351	3,766	345.5
	MG	6.4	56,502	8,828	143.7
	WD	7.5	150,855	20,114	53.6
	$\bar{x}$	6.4	70,866	10,735	161.4
	(SEM)	(± 0.3)	(± 19,353)	(± 2,508)	(± 42.2)

[a] AUC, area under the serum concentration curve
[b] Normalized to 1.73 m^2 surface area

Table 4. Post infusion pharmacokinetic parameters

Dose schedule	Patient	Serum half-lives (h)		V_β (l/m^2)[b]
		α	β	
1.2 mg/m^2/day infusion × 5 days	FV	0.73	5.88	82.6
	RH	0.21	36.00	272.7
	LM	1.77	287.65	769.5
	$\bar{x}$ ± SEM	0.90 ± 0.46	109.84 ± 89.33	374.9 ± 204.8
2.0 mg/m^2/day	NB[a]	–	9.46	142.0
	LL	3.23	56.85	2054.0
	MG	0.11	3.28	36.9
	WD	0.01	8.27	45.4
	$\bar{x}$ ± SEM	1.12 ± 1.06	19.47 ± 12.53	564.6 ± 495.4

[a] Due to the limited number of data points for patient NB the data best fit a monoexponential decay model, $y = 12.63^{e-0.00122t}$; the pharmacokinetic parameters were calculated from this equation
[b] Normalized to 1.73 m^2 surface area

detectable for only 1 h after completion of infusion; massive ascites and lower leg edema were present.

Postinfusion serum samples were obtained in four of six patients in the 2.0-mg/m^2 group. Adequate data points allowed pharmacokinetic analysis in all the patients examined (Table 4), although the kinetic modeling had to be altered in one patient, NB, in whom the limited data points best fit a monoexponential decay model. Serum concentrations of vindesine before termination of the infusion were higher during 2.0-mg/m^2 infusions than during 1.2-mg/m^2 infusions (Fig. 1). Following discontinuation of infusions, vindesine levels generally fell more rapidly in patients who had received 2.0-mg/m^2 infusions. The mean terminal half-life determined in four patients following infusion of 2.0 mg/m^2 (19.5 ± 12.5 h) appeared to be shorter than that observed in three patients after completion of the 1.2-mg/m^2 infusion (109.8 ± 89.3 h), but there was a great deal of overlap (Table 4). By 12 h after discontinuation of the 2.0-mg/m^2 infusion serum concentrations were nondetectable in all four patients. However, serum levels exceeded 2×10^{-9} M at 24, 48, and 72 h after completion of the 1.2-mg/m^2 infusion in two patients (RH and LM) examined at these time points. The volume of distribution

exceeded total body water in all the patients in both groups (Table 4), which suggested avid binding to the tissues.

Average total urinary excretion (Table 5) was similar for all dose schedules (8%–11% of total dose). Measurable amounts of vindesine and its products were detected in the urine up to the latest observation points in each treatment group (144 h after bolus injection and 96 and 72 h following completion of 1.2-mg/m^2 and 2.0-mg/m^2 infusions, respectively). Postinfusion urinary excretion was always less than that excreted during the infusions.

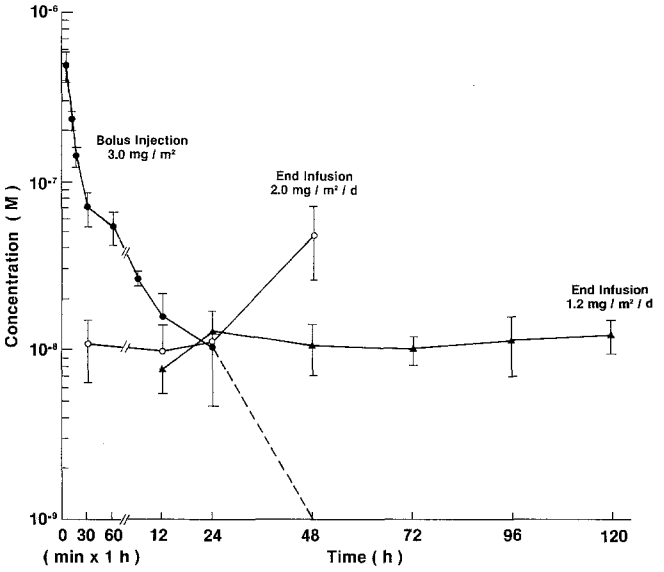

Fig. 1. Comparison of serum concentrations of vindesine (and its metabolic and decomposition products) following 3.0 mg/m^2 IV bolus injection (○———○) in five patients, IV infusion of 1.2 mg/m^2/day for 5 days (△———△) in six patients, and IV infusion of 2.0 mg/m^2/day for 2 days (○———○) in six patients. Mean concentrations ± SEM are plotted at various time points when the majority of patients examined at that time point had serum vindesine levels within the range detectable by the radioimmunoassay ($\geq 1 \times 10^{-9}$ *M*)

No objective antitumor responses (greater than 50% reduction of indicator lesions) were observed in any of the treatment groups. Leukopenia < 2,000 mm^3 occurred in one patient (GS) receiving the 3.0-mg/m^2 bolus injection, two (FH and SM) in the 1.2-mg/m^2 infusion group, and none treated with a 2.0-mg/m^2 infusion. Mild to moderate neurotoxicity developed in one patient (GS, SM, and MG) in each of the treatment groups. Although the sample size is small, comparison of the pharmacokinetic parameters determined in the patients experiencing toxicity and those in patients without toxicity revealed no noteworthy differences. Phlebitis/cellulitis at the site of administration was observed in two of 11 patients who received a peripheral vein infusion, and in none of the five patients who were given a bolus injection.

Discussion

Variations in the pharmacokinetics of vindesine occur with different dose schedules of administration. The terminal half-life following IV bolus injection of 3.0 mg/m^2 was 15.0 ± 9.4 h, wich is within the range observed by other investigators (11.7–24.2 h) [14, 15, 17]. Blood concentrations fell below the assay's range of detectability (~ 1×10^{-9} *M*) by 48 h after bolus injection. In contrast, infusions of either 1.2 mg/m^2/day for 5 days or 2.0 mg/m^2/day for 2 days resulted in sustained serum concentrations > 10^{-9} *M* during the periods of infusion. Similarly, Hande et a. [7] noted prolongation of serum vindesine levels with continuous infusion of 1.5 mg/m^2/day for 2 days in five patients, whereas the serum concentration at 48 h

Table 5. Urinary excretion

Dose schedule	Patient	% of total dose excreted during treatment (period of collection)	% of total dose excreted following treatment (period of collection)[a]	Total (% of total dose) urinary excretion (period of collection)
3.0 mg/m^2 bolus	FV	14.0 (24 h)	3.3 (24 h)	17.3 (48 h)
	GS	1.2 (24 h)	5.4 (144 h)	6.6 (168 h)
	EG	4.3 (24 h)	1.6 (72 h)	5.9 (96 h)
	AN	3.8 (24 h)	–	3.8 (24 h)
	FH	6.6 (24 h)	3.9 (72 h)	10.5 (96 h)
	$\bar{x}$ ± SEM	6.0 ± 2.2	3.6 ± 0.8	8.8 ± 2.4
1.2 mg/m^2/day infusion × 5 days	FV	10.7 (120 h)	–	10.7 (120 h)
	FH	–	–	–
	RW	5.7 (120 h)	–	5.7 (120 h)
	SM	10.9 (120 h)	0.9 (24 h)	11.8 (144 h)
	RH	8.3 (120 h)	1.9 (96 h)	10.2 (216 h)
	LM	12.7 (120 h)	3.1 (24 h)	15.8 (144 h)
	$\bar{x}$ ± SEM	9.7 ± 1.2	2.0 ± 0.6	10.8 ± 1.6
2.0 mg/m^2/day infusion × 2 days	NB	10.3 (48 h)	–	10.3 (48 h)
	LC	9.9 (48 h)	5.2 (24 h)	15.1 (72 h)
	MH	3.2 (48 h)	1.7 (72 h)	4.9 (120 h)
	LL	4.1 (48 h)	–	4.1 (48 h)
	MG	2.3 (48 h)	0.4 (24 h)	2.7 (72 h)
	WD	6.4 (48 h)	3.9 (24 h)	10.3 (72 h)
	$\bar{x}$ ± SEM	6.0 ± 1.4	2.8 ± 1.1	7.9 ± 1.9

[a] The first 24 h-period of urinary excretion was arbitrarily considered to be the 'during treatment' collection for bolus injections

following a bolus injection of 3.0 mg/m^2 in one patient was at the lower limit of sensitivity of the assay.

Continuous IV vindesine infusions of either 1.2 mg/m^2/day for 5 days or 2.0 mg/m^2/day for 2 days resulted in 1.2- to 1.4-fold greater areas under the blood concentration-time curve than IV bolus injection of 3.0 mg/m^2. This increased concentration × time factor might account in part for the antitumor responses noted in some patients receiving vindesine by infusion after failing to respond to bolus injection, as we have previously suggested for vincristine [11].

Following both IV bolus injection and completion of infusions of vindesine, a number of factors suggested avid tissue retention of the agent and its products. The elimination rate constant (k_{31}) was very low compared with the other microscopic rate constants (k_{10}, k_{12}, k_{21}, k_{13}). Also, the volume of distribution greatly exceeded total body water. Extensive tissue binding has previously been suggested for both bolus injection [14, 17] and infusion [12] of this agent.

Urinary excretion accounted for < 20% of the total administered dose of vindesine following both bolus injection and infusion in all of the patients (mean, 8%–11%). Similarly, other investigators have observed low urinary excretion following bolus injection (range, 11%–25% of total dose) [15, 17] and infusion (~ 11% of total dose) [12]. Therefore the biliary tract is probably the major route of elimination of vindesine, as previously observed for vincristine [9]. Hande et al. [7] found a 2.4-fold greater clearance rate of vindesine and its products by the biliary tract compared to the urinary tract.

In summary, the pharmacokinetics of vindesine appear to differ in some respects when this agent is administered by the infusion technique rather than bolus injection. Perhaps these differences might help explain certain clinical events such as the antitumor responses sometimes observed with infusion following failure of bolus injection.

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