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Clinical Pharmacokinetics of Vindesine: Repeated Treatments by Intravenous Bolus Injections*

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Abstract—*Vindesine was administered intravenously to* 12 *patients with advanced cancer. Treatment was repeated after* 2 weeks *or more with a* 1.5- *to* 2-*fold increased dose of vindesine. Five patients received one or two additional injections at the higher dose level. One patient was given* 0.4, 1 *and* 4 mg *of vindesine on days* 1, 3 *and* 6 *and then* 8 mg *on days* 19 *and* 34. *Plasma samples and urine were collected over* 3 days *after injection and monitored for vindesine by radioimmunoassay. Significant time-dependence of vindesine plasma concentration decay kinetics at a constant dose was observed in four patients out of six. The comparison of the kinetics after administration of different doses to the same patient revealed frequent deviations from linearity with no obvious general trend. Urinary excretion was very low* (1–12% *of the dose), and urinary excretion rates correlated with plasma concentrations. Renal clearances were variable from one patient to another and also for the same patient from one injection to another. These data were interpreted in terms of time- and dose-dependence of vindesine pharmacokinetics.*

INTRODUCTION

VINDESINE is a semisynthetic analogue [1] of the naturally occurring vinca alkaloids (vinblastine and vincristine) known to have oncolytic activity in several human neoplasms [2, 3]. Although important improvement of therapeutic safety and efficiency could be achieved by rationalizing dosing and administration schedules on the basis of pharmacokinetic data, much of the distribution, elimination and metabolism of vindesine and generally of the vinca alkaloids in humans remains unknown. Results published so far have demonstrated differences between vindesine, vinblastine and vincristine pharmacokinetics [4] associated with important inter-individual variations of pharmacokinetic parameters [5, 6]. Plasma concentration decay kinetics, which consistently exhibit a rapid initial decline followed by an intermediate phase and a final slower phase, were interpreted in terms of a three-compartment open mamillary model [5, 6]. Some of our preliminary data on long-term vindesine infusion raised questions about the predictive value of this mathematical treatment of kinetic data [7]. Similarly, Jackson *et al.* [8] observed a greater area under the concentration curve in patients receiving vincristine infusions as compared to bolus injections, and Lu *et al.* [9], studying continuous vinblastine infusions, described recently a group of patients with very low clearances, two of them exhibiting a much higher clearance when vinblastine was given as a bolus. These observations prompted us to address the question of possible time- and dose-dependence of vindesine pharmacokinetics.

Twelve patients with advanced cancers were given vindesine (total dose 0.4–4 mg) as bolus intravenous injections. In each case vindesine was well tolerated. Two weeks or more later the same patients were given higher doses of vindesine, six of them receiving one or two additional injections of vindesine at the higher dose level. Plasma samples were collected for 72 hr after administration at time intervals selected to describe as

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accurately as possible plasma concentration decay kinetics [10]. All urine outputs were collected separately for the same period of time. Plasma and urine samples were monitored for vindesine by radioimmunoassay [10]. Results are reported in this paper and discussed in terms of model-independent parameters and direct point-by-point comparison of the different kinetics for the same patient. Urine excretion data are also reported and used for individual renal clearance evaluation.

MATERIALS AND METHODS

Clinical characteristics

Twelve patients undergoing either single-agent vindesine therapy or a combination therapy of vindesine with other anticancer agents (cisplatin, adriamycin) for various neoplastic diseases were studied during their first courses of vindesine therapy. Combination therapy was given 3 days after each vindesine injection. Clinical data about the patients entered in this study are summarized in Table 1. The patients had generally been subjected to prior surgery and/or radiotherapy and some to prior chemotherapy. Vindesine was given as intravenous bolus injections (injection duration <1 min) and did not induce noticeable toxicity. Liver and renal functions were within the normal range for all patients at the time of the study.

Sample analysis

Blood samples were obtained a few minutes before injection then 0.08, 0.17, 0.25, 0.50, 1, 2, 3, 4, 6, 12, 24, 36, 48, 60 and 72 hr after injection. Blood samples were generally collected from a vein on the opposite arm from the injection in heparinized glass tubes and immediately placed at 4°C. The blood was centrifuged at 1000 *g* for 10 min and the resulting plasma was frozen at -30°C until analyzed.

Each plasma sample was analyzed by radioimmunoassay according to the technique described by Rahmani *et al.* [10]. Briefly, plasma was diluted if necessary in phosphate-buffered (50 mM, pH 7.4) saline (0.15 M) containing 1 g/l bovine serum albumin (Fraction V, Sigma, St Louis, MO, U.S.A.) and incubated with antiserum (kindly provided by the Eli Lilly Research Laboratories, Indianapolis, IN, U.S.A.) and ^{125}I-labeled vinblastine-glycyl-L-tyrosine conjugate (synthesized as described in [10]) at 4°C for 22 hr. Human plasma from healthy donors (Centre de Transfusion Sanguine, Marseille, France) was added if necessary to maintain a constant amount of human plasma components in the incubation medium. At the end of the incubation polyethylene glycol 6000 (Merck, Darmstadt, F.R.G.) was added to a final 12.5% (w/v) concentration.

Precipitated immune complexes were separated by centrifugation (2000 *g*, 10 min) and counted for 1 min on a Kontron MR252 γ-counter. Vindesine concentrations were determined by interpolation on the logit–log linearized standard curve (useful range 0.1–20 ng/ml, variation coefficient <15%). Non-specific inhibitions from pre-dose plasma (always less than 10% of control binding) were taken into account to calculate vindesine concentrations (see [10]). Urine outputs were collected separately, volume was measured and an aliquot (about 5 ml) was kept frozen until analyzed. Urine samples were analyzed by radioimmunoassay after dilution (generally 10 times) in phosphate-buffered saline containing bovine serum albumin as described for plasma samples. Pre-dose urine or urine from healthy donors did not produce measurable non-specific inhibitions. Human plasma from healthy donors was added to ensure reproducible precipitation of immune complexes.

Pharmacokinetic analyses

Data processing and pharmacokinetic calculations were performed on a Hewlett-Packard 9825A desk-top computer with the help of a program which allowed linear and log–linear least-squares regression analysis, log–linear interpolations and calculations of areas under concentration–time curves (AUC) according to the trapezoidal rule [11] and to the log–trapezoidal rule [12].

Apparent elimination half-lives were calculated by least-squares regression on terminal plasma concentration data points (from 12 to 72 hr). AUC was calculated based on the trapezoidal rule (the log–trapezoidal rule gave very similar results) and extrapolated to infinite time using the experimentally determined half-life. The small (about 10% of total AUC) portion of the curve between 0 and 0.08 hr was approximated by 0.04 times the vindesine concentration at 0.08 hr. Systemic clearance (Cls) was calculated according to the equation Cls = dose/AUC.

Comparisons of concentration–time curves for a given patient were performed by log–linear interpolation of the plasma concentrations whenever exact sampling times were different. The mean of the plasma concentration ratios was calculated and linear regression analyses were performed.

Cumulated urinary excretion was calculated by summing up the amount of excreted vindesine in the different samples and expressing as a percentage of the dose. Urinary excretion rates were approximated by dividing the amount of excreted vindesine in a micturition by the time

Table 1. *Clinical data*

Patient	Sex	Age	Weight (kg)	Height (cm)	Diagnosis	Combination chemotherapy	Concomitant medications
1	M	59	65	170	chronic lymphoblastic leukemia	none	none
2	M	41	52	170	chronic myeloid leukemia	none	minocycline, erythromycin, allopurinol, cimetidine
3	F	28	54	164	pheochromocytoma	cisplatin	prednisolone, antrafenine
4	F	72	66	154	lymphoma	none	none
5	M	55	75	185	tongue malpighian carcinoma	cisplatin, adriamycin	methylprednisolone, triapride, oxytetracycline
6	M	49	53	172	tongue epidermoid carcinoma	none	penicillin, methylprednisolone oxytetracycline, noramidopyrine
7	F	70	42	146	lacrymal gland adenocarcinoma	none	clonidine
8	F	50	37	156	tongue epidermoid carcinoma	none	ornithine, arginine
9	M	54	81	182	oropharynx malpighian carcinoma	none	none
10	M	64	55	170	tonsil malpighian carcinoma	none	colistine–penicillin G, prednisolone, cefazoline
11	M	46	57	150	tongue epidermoid carcinoma	none	oxytetracycline, midecamycin
12	F	39	40	150	breast adenocarcinoma	none	tiemonium, phloroglucinol

interval from the preceding one. Urinary excretion rates were compared to mean plasma concentrations in the time interval between micturitions (estimated from the area under the concentration–time curve during the time interval, calculated according to the log–trapezoidal rule [12]) by linear regression analysis and by calculating the mean of the excretion rate over plasma concentration ratios.

RESULTS

Plasma concentration decay kinetics

Plasma samples were collected as described in Materials and Methods and analyzed for vindesine by radioimmunoassay using antisera developed by the Eli Lilly Research Laboratories and a ^{125}I-radiolabeled probe for vindesine synthesized as decribed earlier [10]. This assay is characterized by an increased sensitivity (0.05 ng/ml of vindesine) but essentially similar specificity as compared to the original assay described by Root *et al.* [13]. Since no data about vindesine metabolism are yet available, the radioimmunoassay may not be assumed to be strictly specific for the parent compound. However, only vinblastine, vincristine and closely related dimeric alkaloids such as deacetyl-vinblastine cross-react extensively [10, 13]. An example of plasma decay kinetics for patient 1 receiving three successive intravenous bolus injections of vindesine (the first of 4 mg and the second and third of 8 mg) is illustrated in Fig. 1. In accordance to published reports, these kinetics are triphasic. Because of the distinguishable rebound consistently found between 1 and 4 hr, we did not attempt to fit the data to a linear compartmental model. It should be pointed out that similar shapes for plasma decay kinetics can be found in earlier reports [6, 7, 14].

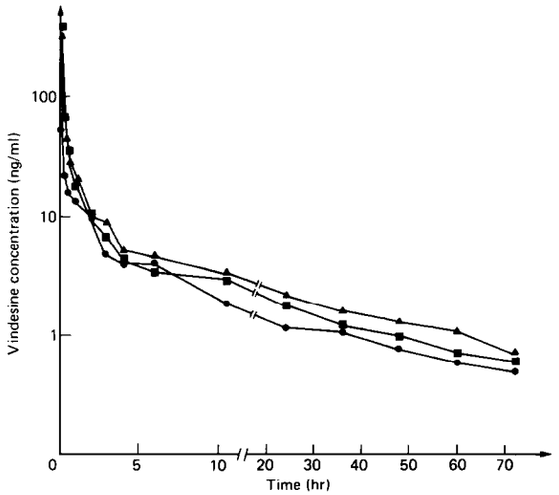

Fig. 1. Patient 1 was given 4 mg on day 1, 8 mg on day 19 and again 8 mg on day 34 of vindesine by bolus injection. Blood samples were collected and analyzed as described in Materials and Methods. Vindesine concentrations are plotted vs time after injection on a long-linear scale (•: first course; ▲: second course; ■: third course).

Systemic clearance and apparent elimination half-life

Apparent elimination half-lives and areas under plasma concentration–time curves (AUC) extrapolated to infinite time were calculated as described in Materials and Methods [11]. Inter-individual variations are reflected by large clearance differences (from 7.0 to 52.1 l/hr) not accounted for by differences in body weight, and variable elimination half-lives (from 8.5 to 36.0 hr). Such differences are typical of vindesine pharmacokinetics, the values being in complete agreement with those reported by Owellen *et al.* [5] and Nelson *et al.* [6]. Clearances and half-lives calculated from the different kinetics of vindesine plasma concentration decay for a single patient were generally comparable (Tables 2 and 3). Exceptions are patients 6 and 11, with clearances differing by about 40%, and patient 5, who exhibited large clearances during the first two courses and decreasing clearances during the third and fourth. At the time of the last injections the patient's health was deteriorating. Patient 12 had a low clearance which increased as doses were increased (from 0.4 to 8 mg). With respect to half-life, large differences were observed only for patients 4 and 7.

Point-by-point comparison of plasma decay kinetics

The apparent stability of clearance and terminal half-lives does not imply that kinetics are time- and dose-independent, since compensating changes in drug distribution and elimination could occur without any large change in systemic clearance. Since, as discussed above, curve fitting to a linear compartment model seemed unrealistic, we made a point-by-point comparison of the vindesine kinetics for the same patient, for either identical or different doses, using logarithmetic interpolation whenever exact sampling times differed (Fig. 2). Linear least-squares regression analysis was then applied to estimate an experimental dose ratio (slope of the regression) and a y-axis intercept that would indicate deviation from proportionality of the two kinetics if statistically different from zero. Such an analysis probably overestimates the importance of the first data points which correspond to large concentrations (see Fig. 1), and to short, thus probably less accurate, time intervals. We have thus also calculated the means of the concentration ratios over the kinetics. This way of

Table 2. Model-independent pharmacokinetic parameters and point-by-point comparison of plasma concentration decay kinetics for identical vindesine doses

Patient	Course No.	Dose (mg)	Cls (l/hr)	$t_{½}$* (hr)	Comparison (course Nos)	Experimental dose ratios calculated from: mean ratio*	slope of regression†	intercept† (ng/ml)	correlation coefficient
1	2	8	32.5	29.0 ± 1.7	3 vs 2	0.96 ± 0.11	1.09 ± 0.07	3.79 ± 5.70	0.973
	3	8	36.6	26.2 ± 2.0		N.S.‡	N.S.	N.S.	
2	2	8	33.0	33.5 ± 1.9	3 vs 2	0.91 ± 0.03	1.00 ± 0.01	−0.98 ± 0.82	0.999
	3	8	36.7	28.8 ± 3.4	4 vs 3	0.05	N.S.	N.S.	
	4	8	32.1	24.2 ± 2.4		1.20 ± 0.09	0.69 ± 0.02	4.76 ± 1.87	0.994
3	2	4	37.5	16.0 ± 2.6	3 vs 2	0.09	0.002	0.07	
	3	4	37.0	16.1 ± 3.1		1.08 ± 0.09	0.65 ± 0.02	2.85 ± 0.90	0.994
4	2	4	32.0	23.8 ± 2.0	3 vs 2	N.S.	0.002	0.04	
	3	4	33.7	20.5 ± 2.2		0.99 ± 0.03	0.92 ± 0.02	0.01 ± 0.78	0.996
5	2	4	50.7	19.3 ± 1.2	3 vs 2	N.S.	0.03	N.S.	
	3	4	38.1	19.3 ± 6.1	4 vs 3	1.35 ± 0.10	1.62 ± 0.02	0.05 ± 0.79	0.999
	4	4	26.0	14.9 ± 0.8		0.04	0.0005	N.S.	
12	4	8	14.7	23.6 ± 1.8	5 vs 4	1.56 ± 0.12	1.43 ± 0.07	4.54 ± 4.04	0.984
	5	8	17.1	23.1 ± 1.4		0.02	0.01	N.S.	
						0.91 ± 0.08	1.51 ± 0.07	−11.59 ± 4.09	0.986
						N.S.	0.01	0.06	

*±S.E.M.
†±S.D.
‡Confidence levels calculated from Gauss inequality; N.S., not significant (>0.2).

Table 3. Comparison of plasma concentration decay kinetics for patients receiving increasing doses

Patient	Course No.	Dose (mg)	Cls (l/hr)	$t_{½}$* (hr)	Dose ratio	Experimental dose ratios calculated from: mean ratio*	slope of regression†	intercept† (ng/ml)	correlation coefficient
1	1	4	26.7	28.7 ± 3.3	2.00	1.76 ± 0.12	2.35 ± 0.14	−6.28 ± 5.27	0.973
	2	8	32.5	29.0 ± 2.0		N.S.‡	N.S.	N.S.	
2	1	4	39.3	36.0 ± 1.0	2.00	2.81 ± 0.30	5.01 ± 0.15	−7.61 ± 2.72	0.994
	2	8	33.0	33.5 ± 1.9		0.06	0.001	0.06	
3	1	2	31.3	14.3 ± 0.6	2.00	1.66 ± 0.13	1.30 ± 0.01	0.31 ± 0.52	0.999
	2	4	37.5	16.0 ± 2.6		0.06	0.0001	N.S.	
4	1	2	27.4	35.2 ± 1.4	2.00	2.14 ± 0.21	2.59 ± 0.06	−0.25 ± 0.39	0.997
	2	4	32.0	23.8 ± 2.0		N.S.	0.005	N.S.	
5	1	2	51.2	29.1 ± 3.1	2.00	2.16 ± 0.19	2.94 ± 0.17	−1.56 ± 2.03	0.975
	2	4	50.7	19.3 ± 1.2		N.S.	0.01	N.S.	
6	1	2	33.6	17.4 ± 0.6	2.00	1.27 ± 0.10	1.79 ± 0.04	−1.76 ± 0.23	0.996
	2	4	51.5	17.0 ± 2.3		0.008	0.02	0.008	
7	1	2.5	31.3	16.6 ± 2.2	2.00	1.96 ± 0.19	1.63 ± 0.14	1.94 ± 2.11	0.964
	2	5	30.1	29.3 ± 2.1		N.S.	N.S.	N.S.	
8	1	3	17.4	9.4 ± 0.4	1.67	2.03 ± 0.18	1.56 ± 0.05	3.60 ± 1.84	0.993
	2	5	16.1	13.4 ± 1.4		N.S.	0.09	N.S.	
9	1	4	42.2	19.6 ± 2.1	1.50	1.57 ± 0.09	1.22 ± 0.06	1.40 ± 1.12	0.985
	2	6	34.3	27.8 ± 1.4		N.S.	0.02	N.S.	
10	1	4	15.3	29.8 ± 5.9	1.50	2.21 ± 0.08	2.67 ± 0.09	−5.85 ± 2.78	0.992
	2	6	11.3	27.9 ± 0.6		0.006	0.003	N.S.	
11	1	4	52.1	21.1 ± 6.6	1.50	1.84 ± 0.19	1.83 ± 0.18	−3.08 ± 10.73	0.931
	2	6	34.9	24.0 ± 7.4		N.S.	N.S.	N.S.	
12	1	0.4	7.1	21.6 ± 4.9	2.5	2.27 ± 0.07	1.98 ± 0.03	0.74 ± 0.26	0.999
	2	1	7.1	24.6 ± 3.4	4.0	0.04	0.002	0.05	
	3	4	10.1	28.1 ± 3.0	2.0	2.47 ± 0.15	2.09 ± 0.04	1.15 ± 0.70	0.997
	4	8	14.7	23.6 ± 1.8	20.0 (4 versus 1)	0.004	0.0004	N.S.	
						1.71 ± 0.14	1.91 ± 0.06	0.20 ± 2.12	0.993
						N.S.	N.S.	N.S.	
						9.94 ± 0.56	7.95 ± 0.25	5.80 ± 2.08	0.995
						0.001	0.0002	0.06	

*±S.E.M.
†±S.D.
‡Confidence levels calculated from Gauss inequality; N.S., not significant (>0.1).

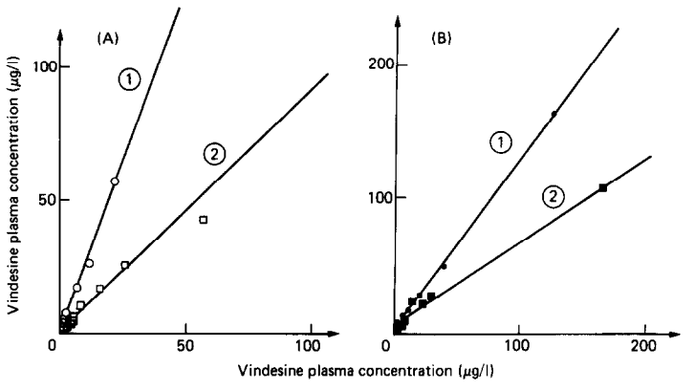

Fig. 2. Vindesine plasma concentrations measured after vindesine injections are plotted vs plasma concentration measured after a previous vindesine injection. The solid lines represent linear least-squares regression analysis of the data. Two examples are shown: patient 4 in part A [second (4 mg) vs first (2 mg) course: ○; third (4 mg) vs second (4 mg) course: □], for which experimental and injected dose ratios are in agreement, and patient 3 in part B [second (4 mg) vs first (2 mg) course: ●; third (4 mg) vs second (4 mg) course: ■], for which experimental dose ratios differ from injected dose ratios. Results of the regression analyses are listed in Tables 2 and 3.

calculating experimental dose ratios gives a much larger weight to longer time data points. Results of these analyses are given in Tables 2 and 3.

Urinary excretion

An example of cumulative urinary excretion and excretion rate vs time plots is shown in Fig. 3. Cumulated excretion was found to be between 1.2 and 12% of the injected dose. Excretion rates were

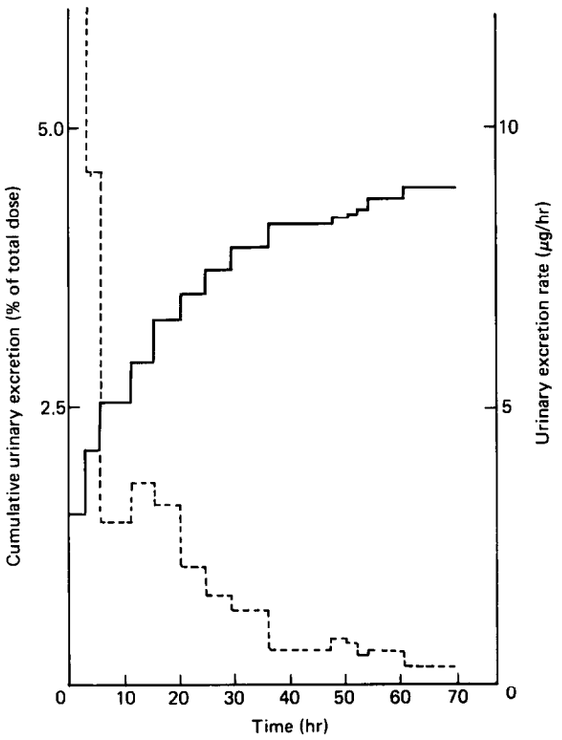

Fig. 3. Vindesine urine concentrations were measured as described in Materials and Methods. Cumulated excretion (solid line) and urinary excretion rates (dashed line), determined as described in Materials and Methods, are plotted vs time for patient 1 (first course: 4 mg).

compared to mean plasma concentrations of the urine collection period calculated from the area under the plasma concentration curve (evaluated by the log-trapezoidal method according to Yeh and Kwan [12]). This method was selected for evaluation of mean plasma concentrations because plasma concentration at the time corresponding to the midpoint of the first urine collection [11], which generally takes place between 1 and 4 hr after injection, underestimates the amount of drug available for renal clearance. With one exception (patient 4, cure 2), there was a good correlation (as judged by the correlation coefficient) between urinary excretion rates and drug concentrations in plasma (Table 4). Slopes of linear least-squares regressions gave an estimation of renal clearance (Table 4). Intercepts were not significantly different ($P < 0.05$) from zero in 13/19 cases, and only five values were large (significantly larger than 0.5 μg/hr; $P < 0.05$). As for the point-by-point comparison of plasma concentrations, it should be pointed out that this kind of analysis gives much weight to short time data for which mean plasma concentrations are less accurate. We thus added to Table 4 the mean of the excretion rate over plasma concentration ratios. Finally, a global estimation of renal clearance is given by the ratio of the total excreted dose to the area under the plasma concentration curve [11] (Table 4).

DISCUSSION

Vinca alkaloids are highly toxic: the vindesine clinical weekly dose, for instance, is about 4 mg/m^3, and vincristine is even more toxic. Optimal doses and administration schedules are

not yet clearly defined. Individual adaptations comparable to what is done for high-dose methotrexate [15] would certainly improve therapeutic efficiency and prevention of toxic side-effects. Thus pharmacokinetic analysis and accurate modeling of distribution and elimination are required. Interpretations of plasma concentration decay kinetics in terms of multiple compartment models achieve satisfactory statistical fittings [5, 6], but linear modeling implies, for observations made on the same patient, that kinetics are identical at a constant dose and that plasma concentrations at any time after administration are directly proportional, to the dose. The present study was intended to test these implications.

As shown in Table 2, fairly different vindesine kinetics were observed for some patients given a constant dose at a few weeks' interval. These differences were rationalized independently of any model by comparison of clearances and by point-by-point comparison of the kinetics. For patient 5, systemic clearance and experimental dose ratios indicated an evolution of vindesine kinetic behavior. For patients 2 (cures 3 and 4), 3 and 12 differences were less obvious and were reflected only by the experimental dose ratios evaluated by linear regression. To be very conservative, time-dependence would be considered as significant only when both estimations of dose ratio are significantly different from 1. Besides, since the distributions of concentration ratios were not strictly normal, Gauss inequality was used instead of Student's t test for assessing statistical signification. Then patient 5 demonstrated significant time-dependence at a confidence level better than 4%. The meaning of deviations observed with patients 2, 3 and 12 was less clear. However, when reasoning in terms of Bonferroni simultaneous inferences, these differences could be considered as significant (confidence level 5%), and kinetics were stable only in patients 1, 2 (cures 2 and 3) and 4.

The same statistical analysis was applied when patients were given increasing doses of vindesine. Again, as shown in Table 3, significant deviations between injected and calculated dose ratios were observed. Experimental dose ratios for patients 2 and 10 were larger than ratios of injected doses (confidence levels better than 6 and 0.6%, respectively). For patients 3, 6 and 12 they were smaller (confidence levels better than 6 and 2% for patients 3 and 6 and better than 4 and 0.4% for patient 12 between cures 1 and 2 and between cures 2 and 3). Kinetics in patients 1, 7, 8, 11 and 12 (between cures 3 and 4) did not differ significantly from linearity. A systematic trend would have been expected which could correlate with saturation or activation of some transport or metabolic pathways. The absence of such a trend

Table 4. Urinary excretion of vindesine

Patient	Course No.	Dose (mg)	AUC (μg/hr/l)	% excreted	Excreted/AUC (l/hr)	Mean ratio* (l/hr)	Slope† (l/hr)	Intercept† (μg/hr)	Correlation coefficient
1	1	4	149.8	4.5	1.29	1.19 ± 0.09	1.03 ± 0.04	0.36 ± 0.25	0.989
	2	8	258.9	2.3	0.71	0.68 ± 0.07	1.44 ± 0.07	−1.92 ± 0.25	0.985
	3	8	225.3	1.6	0.57	0.85 ± 0.07	0.37 ± 0.02	0.95 ± 0.20	0.980
2	1	4	96.6	5.3	2.08	1.72 ± 0.33	4.75 ± 0.14	−2.59 ± 0.45	0.994
	2	8	213.9	2.0	0.67	0.85 ± 0.06	0.84 ± 0.02	0.00 ± 0.33	0.997
	3	8	217.9	4.2	1.54	1.77 ± 0.09	1.77 ± 0.03	0.16 ± 0.25	0.998
	4	8	250.8	4.9	1.56	1.59 ± 0.09	1.94 ± 0.02	−0.45 ± 0.21	0.999
3	1	2	63.9	1.3	0.41	0.81 ± 0.10	0.13 ± 0.20	0.33 ± 0.05	0.904
	2	4	106.5	3.8	1.42	1.57 ± 0.07	1.46 ± 0.02	−0.21 ± 0.12	0.998
	3	4	108.6	4.2	1.55	1.33 ± 0.07	1.62 ± 0.03	−0.23 ± 0.10	0.995
4	1	2	72.9	2.0	0.55	0.59 ± 0.11	1.87 ± 0.15	−0.89 ± 0.16	0.938
	2	4	124.9	1.3	0.42	0.69 ± 0.13	0.32 ± 0.13	0.90 ± 0.84	0.547
	3	4	118.7	2.0	0.67	0.85 ± 0.10	1.06 ± 0.04	−0.38 ± 0.18	0.990
5	1	2	38.1	1.8	0.92	1.00 ± 0.23	1.17 ± 0.18	0.13 ± 0.22	0.860
	2	4	79.0	2.2	1.12	1.33 ± 0.21	1.24 ± 0.07	0.29 ± 0.28	0.980
	3	4	105.0	3.0	1.14	2.14 ± 0.42	0.85 ± 0.07	0.56 ± 0.20	0.971
	4	4	153.9	2.3	0.60	1.07 ± 0.14	0.44 ± 0.10	0.69 ± 0.40	0.801
6	1	2	59.5	1.2	0.40	0.74 ± 0.18	0.71 ± 0.03	−0.09 ± 0.12	0.994
	2	4	77.7	4.1	2.11	4.04 ± 0.96	2.04 ± 0.17	0.91 ± 0.60	0.956
12	1	0.4	56.3	11.9	0.85	0.88 ± 0.04	1.12 ± 0.06	−0.18 ± 0.06	0.980
	2	1	140.1	8.7	0.62	0.76 ± 0.07	1.05 ± 0.15	−0.53 ± 0.37	0.886
	3	4	396.0	8.2	0.83	0.99 ± 0.02	0.94 ± 0.10	0.54 ± 0.63	0.903
	4	8	544.2	7.8	1.15	1.02 ± 0.10	0.97 ± 0.12	0.29 ± 0.95	0.916
	5	8	467.7	10.5	1.80	1.82 ± 0.15	3.19 ± 0.10	−6.02 ± 1.26	0.992

*±S.E.M.
†±S.D.

in these results may be explained by the time-dependence of the kinetics. Further interpretations would require an extensive set of observations. Besides, only increasing doses have been studied as no indication of toxic effects, and thus no reason to reduce injected doses, appeared.

Urinary excretion was very low: total urine excretion (monitored over 65–72 hr after injection) was between 1.2 and 12% of the dose, thus lower than that reported by Owellen *et al.* [5]. We have no explanation for this discrepancy as the assays used had similar specificities [10]. Very low renal clearances have been reported by others [16]. Excretion rates and plasma concentrations were correlated, indicating that vindesine is slowly filtered through the kidney. This correlation and the overall agreement of the three different estimations of renal clearance (Table 4) may be considered as indirect arguments against extensive interference of some unknown vindesine metabolite in the assay, since differential renal excretion of vindesine and of the metabolite would then have been expected. Important variations from one patient to another, but also for the same patient between different cures, were observed (see, for instance, patient 6). They cannot explain modifications of systemic clearances but they nevertheless reflect the instability of vindesine kinetics and call for further study of vindesine binding to blood-soluble and formed elements, as previously described for vinblastine [17] and vincristine [18].

In conclusion, vindesine pharmacokinetics cannot be usefully described by linear compartmental models as time-dependent and non-linear phenomena occur. Deviations are not systematic and explanations should probably be looked for in a detailed analysis of distribution, elimination and metabolism which should be initiated at the *in vitro* cellular level. These data are in complete agreement with unsuccessful attempts to predict plasma concentrations during long-term infusion on the basis of pharmacokinetic parameters determined in advance after bolus injections.

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