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Pharmacokinetics of vincristine, vinblastine, and vindesine in rhesus monkeys

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Summary. *The pharmacokinetics of vincristine, vindesine, and vinblastine following IV bolus doses of 0.05 mg, 0.10 mg, and 0.20 mg/kg body weight, respectively, were studied in adult male rhesus monkeys. The alkaloid concentrations were determined by a sensitive radioimmunoassay. Pharmacokinetic data were analyzed by a non-linear least-square regression program NONLIN, and the data fit a two-compartment open model. The average terminal half-lives of vincristine, vinblastine, and vindesine in the serum were 189, 152, and 175 min, respectively. The areas under the alkaloid concentration-time curve from 0 to ∞ for these drugs for a 1-mg dose were as follows: vincristine, 26,572 nM · min; vinblastine, 16,745 nM · min; and vindesine, 12,708 nM · min. The clearance rate (ml/min/kg) for vincristine (4.8) was slightly lower than that for vinblastine (7.0) or vindesine (7.8). The apparent volumes of distribution for vincristine, vinblastine, and vindesine were, respectively, 1.3, 1.5, and 1.9 l/kg body weight. In the two-compartment open model, the transfer rate constant from compartment 2 to compartment 1 (k_{21}) was lower than the other rate constants (k_{10} and k_{12}) for each of the alkaloids. The total average excretion of the alkaloids over a 4-day period in urine and feces for vincristine, vinblastine, and vindesine were, respectively, 36.7%, 18.2%, and 25.3% of the injected dose. These data indicate avid tissue retention of the Catharanthus alkaloids in this non-human primate. The similarities between these pharmacokinetic parameters and those previously reported for man suggest that the rhesus monkey is an ideal animal model in which to study the pharmacologic properties of these alkaloids.*

Introduction

The dimeric alkaloids vincristine and vinblastine, which contain indole-indoline moieties from *Catharanthus* plant species, are widely used as antitumor agents, singly or in combination with other chemotherapeutic agents. These alkaloids differ only slightly in structure; specifically, the methyl group on the vindoline N atom in vinblastine is substituted by a formyl group in vincristine, but they have profound differences in their toxicities, dosages, and clinical activities [9, 12, 19, 21]. Vinblastine is widely used in the treatment of Hodgkin's disease and testicular neoplasms, whereas vincristine exhibits activity in both non-Hodgkin's and Hodgkin's lymphomas, acute lymphoblastic leukemia, Wilms' tumor, and rhabdomyosarcoma. Neuropathy has been most frequently observed following vincristine administration, whereas myelosuppression has been the dose-limiting toxicity for vinblastine. Recently, a semisynthetic derivative of vinblastine, 4-deacetyl-vinblastine 3-carboxyamide (vindesine), has been undergoing extensive clinical phase-II trials [8, 9]. The clinical dosages of IV bolus injections of vincristine, vindesine, and vinblastine are approximately 1.0 mg/m^2, 2.5 mg/m^2, and 5.0 mg/m^2, respectively. The pharmacological bases of these differences among the alkaloids are not well understood. This study was undertaken to investigate comparative pharmacokinetics of these alkaloids in rhesus monkeys using clinically relevant dosages.

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Materials and methods

Rhesus monkeys. The male rhesus monkeys *(Macaca mulatta)* used in this study were kindly donated by Dr Thomas B. Clarkson of the Department of Comparative Medicine of Bowman Gray School of Medicine. The animals were kept in individual metabolic cages in a windowless room, artificially lighted from 6 a.m. to 5 p.m., and maintained at 72° F–78° F with 12 air changes/h. These monkeys had normal liver and kidney functions as evaluated by serum creatinine levels and serum glutamate oxalacetate transaminase activities, and were free of any obvious pathological symptoms. They were fed Purina Monkey Chow 25 (Ralston Chow Company, St Louis, MO) ad lib.

Alkaloid administration and collection of blood, urine, and feces samples. The animals were immobilized by IM injection of 5–10 mg/kg body weight of ketamine hydrochloride (Bristol Laboratories, Syracuse, New York). Monkeys #128 and #199 received injections in the saphenous vein of vincristine sulfate (Oncovin, Eli Lilly & Co., Indianapolis, IN) 0.05 mg/kg body weight with a #23 butterfly needle. The injections were completed within a period of 1–2 min. Monkeys #492 and #722 were given a similar IV bolus injection of vinblastine sulfate (Eli Lilly & Co.) 0.2 mg/kg body weight. Monkeys #722, #199, and #128 received vindesine sulfate (Eli Lilly & Co.), 0.1 mg/kg body weight. After each injection there was an interval of 3–4 weeks before the next. Blood samples were withdrawn from the femoral vein at 2, 5, 10, 15, 30, and 60 min and 2, 4, 6, 24, 48, and 72 h. The samples were kept on ice and centrifuged at 3,000 rpm for 15 min within 1–2 h, and the resultant sera were stored at −20° C. Cumulative 24-h urine and feces samples were collected for 4 successive days. Urine volume was noted and an aliquot stored at −20° C. Daily feces

samples were suspended in 500 ml 0.05 N H_2SO_4 and homogenized in a Waring Blender at low speed. Total volume was noted, and an aliquot was centrifuged at 7,000 rpm for 15 min. The clear supernatant was stored at −20° C.

Determination of vincristine, vindesine, and vinblastine. The alkaloid content in the urine, feces, and blood samples was determined by a sequential saturation radioimmunoassay [23]. Vincristine sulfate (NSC-67574) and vinblastine sulfate (NSC-49842) were obtained from Dr John Douros of the National Cancer Institute, Bethesda, MD. Radioactive ^{3}H-vinblastine sulfate (specific activity, 10.5 Ci/mmol) and ^{3}H-vincristine sulfate (specific activity 3.2 Ci/mmol) were purchased from Amersham/Searle Corp., Arlington Heights, IL. Vincristine sulfate, vindesine sulfate, vinblastine sulfate, and the radioactive alkaloids were more than 95% pure as analyzed by thin-layer chromatography on silica gel plates using solvent systems of diethylether : n-propyl alcohol : triethylamine (24 : 16 : 2, v/v/v) and chloroform : methanol : formic acid (70 : 30 : 5, v/v/v/). The alkaloids were also analyzed by high-pressure liquid chromatography in an Ultrasphere-ODS (C_{18}), 5-μm, reverse-phase column with methanol : water : triethylamine (500 : 300 : 1.5, v/v/v) as solvent system, 254 nm detector and a flow-rate of 1.4 ml/min. Vincristine, vindesine, and vinblastine gave single peaks at 13.0 min, 17.0 min, and 19.7 min retention time, respectively. Vincristine sulfate, vindesine sulfate, and vinblastine sulfate in mass spectroscopic analysis on Riber Mag RT-10, GC-MS gave sharp single peaks of the base as MH+ ion mass of 826, 755, and 812, respectively. For the radioimmunoassay, a standard curve was always obtained with each experiment. The mean values for 50% competition levels of these alkaloids in a typical experiment were in the range of 0.4−0.6 ng. In the reconstituted samples of serum, urine, or feces to which known amounts of the labeled or unlabeled alkaloid were added, recovery of the alkaloids was more than 90%. The alkaloid content of all the commercial lots of vincristine sulfate, vindesine sulfate, and vinblastine sulfate used in this study were always verified by the radioimmunoassay. The alkaloid content was presented in terms of alkaloid equivalents, which contained the parent alkaloid along with degradation and/or metabolic products.

Data analysis. Inspection of the drug concentration-time data plotted on semilogarithmic paper revealed a biexponential decay pattern. Initial pharmacokinetic parameter estimates were obtained by a modified CSTRIP program [20] to yield the apparent volume of the central compartment (V_c) along with the microscopic rate constants. These data further analyzed by means of a nonlinear least-square regression program NONLIN [13] in conjunction with a specific subroutine for a two-compartment open model. The biexponential decay can thus be expressed by Eq. (1):

$$C_1 = A_1 e^{-\alpha t} + A_2 e^{-\beta t}, \qquad \text{(Eq. 1)}$$

where C_1 is the serum drug concentration at time t, A_1, and A_2 are the intercepts on the ordinate at time zero, and α and β are the first-order disposition rate constants. A weighting function of $1/C_1$ was used in the NONLIN analysis. The microscopic rate constants (k_{10}, k_{12}, and k_{21}) in the model were calculated by NONLIN computer program [13]. The biological half-life ($t_{1/2}$) of the serum alkaloid was calculated from the equation: $\beta t_{1/2} = 0.693$/terminal rate constant. The area under the serum concentration-time curve from time zero to infinity (AUC_0^∞) was determined from Eq. (2):

$$AUC_0^\infty = \frac{A_1}{\alpha} + \frac{A_2}{\beta}. \qquad \text{(Eq. 2)}$$

Plasma clearance was calculated by Eq. (3):

$$\text{Plasma clearance} = \frac{\text{Dose}}{AUC_0^\infty}. \qquad \text{(Eq. 3)}$$

Apparent volume of the central compartment (V_c) and the apparent volume of distribution (V_D) were calculated by Eqs. (4) and (5):

$$V_c = \text{Dose}/A_1 + A_2 \qquad \text{(Eq. 4)}$$

$$V_D = \frac{\text{Dose}}{AUC_0^\infty \times \text{Terminal rate constant}}. \qquad \text{(Eq. 5)}$$

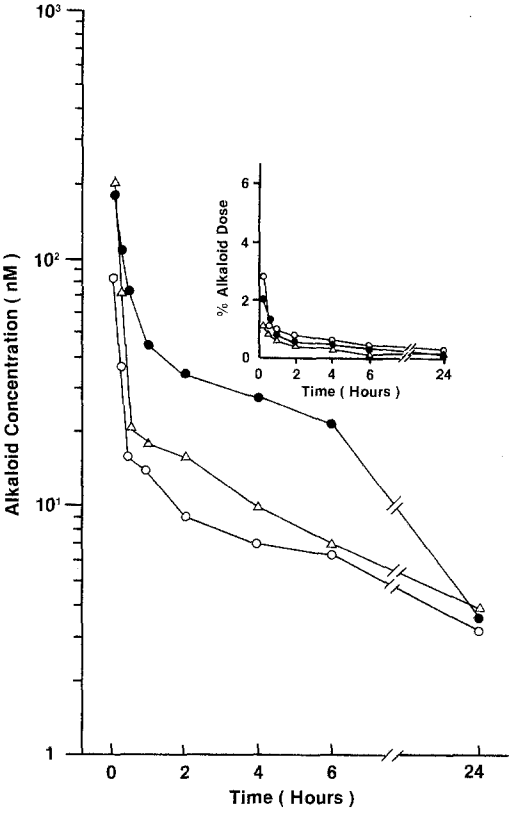

Fig. 1. Semilogarithmic plots of serum vincristine, vinblastine, and vindesine concentrations versus time in rhesus monkeys. The serum alkaloid concentrations (nM and ± SD) at 2, 5, 10, 30, and 60 min and 2, 4, 6, and 24 h in four separate experiments were as follows: vincristine sulfate (monkey #199, dose 0.05 mg/kg body weight), 239 ± 140, 85 ± 34, 37 ± 19, 16 ± 8, 14 ± 5, 9.3 ± 3.3, 7.1 ± 0.9, 6.5 ± 1.5, and 3.2 ± 1.2, respectively; vinblastine sulfate (monkey #492, dose 0.2 mg/kg body weight), 556 ± 238, 181 ± 71, 109 ± 62, 74 ± 40, 45 ± 17, 35 ± 8, 27 ± 12, 22 ± 9, and 3.5 ± 0.7, respectively; vindesine sulfate (monkeys #772 and #128, dose 0.1 mg/kg body weight) 2-min value omitted, 200 ± 82, 72 ± 59, 33 ± 23, 21 ± 14, 18 ± 8, 16 ± 1, 10 ± 4, 7.0 ± 3, 3.9 ± 1.3, respectively. Body serum volume was assumed to be 4% of body weight for calculation of total alkaloid content in the serum. In the *insert* data on percent alkaloid dose in the serum versus time are plotted. ○———○ vincristine, (●———●) vinblastine; and (△———△) vindesine

These data were normalized to per kilogram body weight. The AUC_0^∞ data were also normalized to 1-mg doses of the alkaloids.

Results

On IV bolus injection of vincristine (0.05 mg/kg), vindesine (0.10 mg/kg), or vinblastine (0.20 mg/kg) in rhesus monkeys serum alkaloid concentration versus time data from four separate experiments for each alkaloid revealed a rapid decline in the alkaloid concentrations during the initial 30 min, followed by a slower decline (Fig. 1). At 5 min after injection serum concentrations (mean ± SD) of 85 ± 34, 200 ± 81, and 181 ± 71 nM were obtained for vincristine, vindesine, and vinblastine, respectively. The alkaloid concentrations were not always detectable in the samples drawn at 24 h and beyond.

The pharmacokinetic data fit into a two-compartment open model. In this model, the mean terminal half-lives ($\beta t_{1/2}$) for vincristine, vindesine, and vinblastine were 189 min, 175 min, and 152 min, respectively (Table 1). The half-life of the initial decay phase ($\alpha t_{1/2}$) of each alkaloid was 2–3 min. The apparent volumes of the central compartment (V_c) for these alkaloids were between 127 and 210 ml/kg, and the apparent volumes of distribution (V_D) for vincristine, vindesine, and vinblastine were 1.31, 1.92, and 1.50 l/kg, respectively. Areas under the alkaloid concentration-time curve from zero to infinity (AUC_0^∞) for 1 mg alkaloid for vincristine, vindesine, and vinblastine were, 26,572 nM · min, 12,708 nM · min, and 16,745 nM · min, respectively. The plasma clearance rate of vincristine (4.8 ml/min/kg) was less than that of vindesine (7.6 ml/min/kg) or vinblastine (7.0 ml/min/kg). In the two-compartment open model, the rate of drug transfer from compartment 2 to compartment 1 (k_{21}) for each alkaloid was always lower than k_{10} or k_{12} (Table 1).

Excretion of the alkaloids in urine and feces over a 4-day period was investigated in eight to nine separate experiments for each alkaloid (Tables 2–4). The results showed that only about one-third to one-fifth of the injected doses was excreted, and more than 95% of the excretion took place in the first 24–48 h (data not shown). By 72–96 h there were very low (< 2%) to undetectable concentrations of the alkaloid in the urine and feces. These results further indicated that in most of the experiments vincristine was excreted more in the feces than in the urine (Table 2), whereas vinblastine was always excreted more in the urine than in the feces (Table 4). In case of vindesine, however, there appeared to be no preferential excretion of the alkaloid by either route (Table 3).

Table 1. Pharmacokinetic parameters of the *Catharanthus* alkaloids in rhesus monkeys

Drug	$\alpha t_{1/2}$ (min)	$\beta t_{1/2}$ (min)	V_c (l/kg)	V_D (l/kg)	AUC_0^∞ (nM · min)	AUC_0^∞ (nM · min/mg)	Plasma Clearance (ml/min/kg)	k_{10} (min^{-1})	k_{12} (min^{-1})	k_{21} (min^{-1})
Vincristine	2.6	189	0.143	1.31	11,274	26,572	4.8	0.059	0.189	0.016
Vindesine	2.2	175	0.127	1.92	13,979	12,708	7.6	0.094	0.204	0.012
Vinblastine	1.9	152	0.210	1.50	31,146	16,745	7.0	0.054	0.281	0.031

Table 2. Excretion of vincristine, expressed as percent dose, in urine and feces from rhesus monkeys over a period of 4 days after a single IV bolus injection (dose = 0.05 mg/kg body weight)

Experiment #	Monkey # 128			Experiment #	Monkey # 199		
	Urine[a]	Feces[a]	Total[a]		Urine[a]	Feces[a]	Total[a]
1	13.9	11.2	25.1	5	2.7	11.7	14.4
2	12.0	13.8	25.8	6	4.5	49.9	54.4
3	11.9	25.8	37.7	7	6.9	36.5	43.4
4	12.2	30.7	42.9	8	8.5	41.6	50.1
Mean	12.5	20.4	32.9		5.6	34.9	40.6
SD	0.9	9.4	8.8		2.6	16.4	18.0

[a] Means: urine = 9.1; feces = 27.6; total = 36.7

Table 3. Excretion of vindesine, expressed as % dose, in urine and feces from rhesus monkeys over a period of 4 days after a single IV bolus injection (dose = 0.10 mg/kg body weight)

Experiment #	Monkey # 722			Experiment #	Monkey # 199			Experiment #	Monkey # 128		
	Urine[a]	Feces[a]	Total[a]		Urine[a]	Feces[a]	Total[a]		Urine[a]	Feces[a]	Total[a] ,,
1	5.8	11.2	17.0	4	11.9	13.4	25.3	7	7.7	7.1	14.8
2	9.8	5.0	14.8	5	16.8	47.0	63.8	8	12.8	10.6	23.4
3	8.8	13.5	22.3	6	9.0	18.9	27.9	9	9.8	8.4	18.2
Mean	8.1	9.9	18.0		12.6	26.4	39.0		10.1	8.7	18.8
S.D.	2.1	4.4	3.8		3.9	18.0	21.5		2.5	1.8	4.3

[a] Means: urine = 10.3; feces = 15.0; total = 25.3

Table 4. Excretion of vinblastine, expressed as % dose, in urine and feces from rhesus monkeys over a period of 4 days after a single IV bolus injection (dose = 0.20 mg/kg body weight)

Experiment #	Monkey # 492			Experiment #	Monkey # 722		
	Urine[a]	Feces[a]	Total[a]		Urine[a]	Feces[a]	Total[a]
1	20.7	2.9	23.6	5	7.7	3.5	11.2
2	4.6	2.3	6.9	6	1.5	1.8	3.3
3	10.2	9.6	19.8	7	14.5	12.3	26.8
4	17.6	6.6	24.2	8	14.6	14.9	29.5
Mean	13.3	5.3	18.6		9.6	8.1	18.0
SD	7.3	3.4	8.0		6.3	6.4	12.7

[a] Means: urine = 11.4; feces = 6.7; total = 18.3

Discussion

Tritium-labeled alkaloids have been used to investigate the preliminary pharmacology of vincristine [3, 4, 7], vinblastine [1, 2, 5], and vindesine [6] in rodents [1, 2, 4, 6, 7], dogs [4, 5], and rhesus monkeys [7]. Serum pharmacokinetics of vincristine [3, 10, 14, 17, 22, 25], vinblastine [14–16], and vindesine [14, 17] have been studied in cancer patients by using tritium-labeled alkaloid [3, 10, 15] or unlabeled drug [14, 16, 17, 22, 25]. In humans in whom serum alkaloid concentrations have been determined up to 48 h and beyond (96–120 h), the pharmacokinetic data fit into a three-compartment open model [14, 16, 22, 25], and the biological half-lives of these alkaloids have been in the range of 20–85 h. When, however, the data are analyzed up to 6 h or to earlier time points [3, 6, 7, 17] the pharmacokinetic data fit a two-compartment open model, and shorter terminal half-lives are obtained [4–7, 10]. Our data in the rhesus monkeys, with shorter terminal half-lives (152–189 min), are consistent with similar analysis for vincristine in humans [3], dogs [4], and rhesus monkeys [7]. Moreover, our findings of a longer terminal half-life, lower clearance rate, and higher AUC_0^∞ for vincristine than for vinblastine are qualitatively in agreement with the results of Nelson et al. [14] in humans. Our estimated pharmacokinetic parameters for vindesine, however, are qualitatively slightly at variance with those obtained in humans [14], which may be due to differences in dose and in the number of samples for pharmacokinetic analysis. Furthermore, our finding that k_{21} is a rate-limiting step among the microscopic rate constants in a two-compartment open model are in agreement with k_{31} as a rate-limiting step in a three-compartment open model [14, 22, 25]. These data, therefore, suggest avid binding of the alkaloids to the tissues.

If body plasma volume is assumed to be 4% of body weight, when pharmacokinetic data are plotted as percent alkaloid dose in the plasma versus time (Fig. 1, *insert*) it is clear that there is less than 1% alkaloid in the plasma by 1 h after injection. These data further support the notion that the major portion of the alkaloids is avidly bound to the body tissues.

The use of radioactive alkaloid has led to reports that biliary excretion is a major route of vincristine elimination in rodents [1, 2, 4], dogs [4], and humans [10]. Our finding of higher vincristine excretion in feces is in agreement with these results. Our results for excretion of vincristine in urine are further in agreement with the data obtained in humans [3, 10, 17, 22]. Excretion data for vindesine in cancer patients (D. V. Jackson et al. 1983, submitted for publication) are also in the same range as obtained in this study. Our finding of higher excretion of vinblastine in urine than in the feces, however, is at variance with the published data in dogs [5] and rodents [2]. Nevertheless, our finding that only one-third to one-fifth of the administered dose is excreted is consistent with the data obtained with vincristine [3, 4, 6], vinblastine [1, 2, 4, 5], and vindesine (D. V. Jackson et al. 1983, submitted for publication).

Factors responsible for preferential excretion of vinblastine in the urine, and vincristine in the feces are not known [10, 17]. Metabolism of these alkaloids, on which there is limited information [1, 4–7, 16, 24], may be one of the factors.

In conclusion, there appear to be various differences in the pharmacokinetics of vincristine, vinblastine, and vindesine in rhesus monkeys. The comparatively higher serum AUC values of vincristine than vinblastine following IV bolus injection may explain the increased toxicity of vincristine in patients and experimental animals despite a 4- to 5-fold lower dose. Avid tissue binding of each of these alkaloids, similar to that reported in cancer patients, suggests that the rhesus monkey is an ideal animal model for further investigation of the pharmacokinetics of these agents. It is important to note that among large animals, rhesus monkeys show neurotoxic symptoms [26] similar to those caused in humans by vincristine. Since the alkaloid content in serum is less than 1% of the dose and since there is only one-third to one-fifth excretion of the injected dose, it appears important to conduct studies of the systematic tissue distribution pharmacokinetics and metabolism of these alkaloids to allow better understanding of the differences in their pharmacologic properties.

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