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Pharmacokinetics of Vincristine Sulfate in Children

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Summary. *A radioimmunoassay was used to measure vincristine sulfate concentrations in the serum of four children with malignancies (ages 5–16 years) following intravenous (IV) bolus injections. The pharmacokinetic data were analyzed by a non-linear least-square regression program NONLIN. A three-compartment open model fitted the raw data better than a two-compartment model in three patients. In the other patient the raw data fitted a two-compartment open model. The half-lives of the triphasic decay curves α, β, and γ were 2.6, 41, and 1,531 min (25.5 h), respectively. The mean apparent volume of the central compartment was 3.25 l, and the volume of distribution per 1.73 m^2 body surface area at steady state was 215.9 l. In a three-compartment open model, the first-order distribution and elimination rate constants (min^{-1}) of vincristine were as follows: k_{12}, 0.088; k_{13}, 0.121; k_{21}, 0.028; k_{31}, 0.0026; k_{10}, 0.045. The plasma clearance was 146.2 ml/min per 1.73 m^2, while the AUC_0^∞ was 27,816 nM · min. Urinary excretion in one patient demonstrated a drug concentration of $>1.0 \times 10^{-7}$ M in the urine up to 78 h after the injection. Up to 37% of the administered drug was excreted in the urine as vincristine and/or its metabolites by 90 h. The low elimination rate constant from poorly perfused tissues to blood plasma (k_{31}), a large apparent volume of distribution, and a long biological half-life (25.5 h) indicate avid tissue binding from which a slow release of the drug from the body tissues occurs.*

Introduction

The dimeric alkaloids, vincristine and vinblastine, containing indole-indoline moieties from *Catharanthus* species are widely used as antitumor agents, singly or in combination with other chemotherapeutic agents. These alkaloids differ only slightly in structure, namely the methyl group on the vindoline N-atom in vinblastine is substituted by a formly group in vincristine, but they have profound differences in their toxicities, dosages, and clinical activities [1, 7]. Vinblastine has been most widely used in the treatment of Hodgkin's disease and testicular neoplasms, whereas vincristine exhibits substantial activity in both non-Hodgkin's and Hodgkin's lymphomas, acute lymphoblastic leukemia, Wilms' tumor, rhabdomyosarcoma, and neuroblastoma. Neuropathy has been most frequently observed following vincristine administration, whereas myelosuppression has been the dose-limiting toxicity for vinblastine [7, 15]. The mechanisms underlying these toxicities are not fully understood. Vincristine is generally better tolerated in children than in adult patients. Pharmacokinetics of vincristine sulfate in adult patients have been reported [2, 10, 13, 19]. Clinical pharmacology of antitumor drugs in pediatric patients has been largely ignored [4], and there is no information on the clinical pharmacokinetics of vincristine in children. In this paper we describe the pharmacokinetics of vincristine sulfate following IV bolus injection in four pediatric patients.

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Materials and Methods

Patients. Characteristics of the pediatric patients with respect to their sex, age, weight, height, dose, disease, other concomitant drugs, and vincristine sulfate dose administered are described in Table 1. The child with rhabdomyosarcoma (subject 1) had received prior irradiation and $1^1/_2$ years of multi-agent chemotherapy (including vincristine) for a stage III nasopharyngeal mass. The patient with non-Hodgkin's lymphoma had received 4 weeks of chemotherapy (including vincristine) prior to entry on the present study. The two children (subjects 3 and 4) diagnosed as having acute lymphocytic leukemia had not received prior therapy. Subject 3 achieved a complete remission with vincristine and

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Table 1. Patient characteristics

Subject no.	Sex	Age (years)	Weight (kg)	Height (cm)	BSA[a] (m^2)	Dose		Other concomitant drugs	Disease
						mg	mg/m^2		
1	F	6.5	18.18	113.0	0.769	1.4	1.82	Cytoxan, actinomycin D	Rhabdomyosarcoma
2	F	9	34.10	137.1	1.154	2.0	1.73	Prednisone	Non-Hodgkin's lymphoma
3	F	16	50.90	162.6	1.524	2.0	1.31	Allopurinol, prednisone	Acute lymphocytic leukemia
4	M	5	18.86	115.6	0.791	1.6	2.02	Allopurinol, prednisone	Acute lymphocytic leukemia

[a] Body surface area

prednisone, while the other child (subject 4) proved to be refractory to 6 weeks of vincristine and prednisone. Pretreatment serum levels of bilirubin, blood urea nitrogen and creatinine were normal in each patient. Informed consent for this investigation was obtained.

Vincristine Administration and Collection of Blood and Urine Samples. A heparin lock employing a no. 23 gauge butterfly needle (Abbott Company, Chicago, IL) was inserted into a vein of the opposite arm, or below the site of vincristine administration. Vincristine was administered by IV bolus injection over a period of approximately 1 min as vincristine sulfate for injection, USP (Oncovin), Lilly and Co., Indianapolis, IN, USA. After the IV bolus injection, 2- to 3-ml blood samples were withdrawn at the following time points for the various patients: (1) 3, 9, 12, 15, 20, 30, 45, 60 min and 2, 4, 6, 24, and 48 h; (2) 1, 3, 6, 9, 12, 15, 20, 30, 45, 60 min and 2, 4, 7, 24, and 49 h; (3) 1, 5, 10, 15, 20, 30, 60 min and 2, 4, and 24 h; (4) 3, 9, 20, 30, 45, 60 min and 5, 8, 7, and 24 h. A blood sample was also taken prior to the drug injection. The blood samples were protected from light and placed in a refrigerator prior to their delivery to the laboratory. The samples were centrifuged within 1–2 h after withdrawal at 3,000 rpm for 15 min and the clear supernatants were stored at −20° C. The total voided urine for patient BS after IV drug administration was collected every 6 h up to 78 h, and an additional 12-h sample was also collected. For patient JL, urine was collected every 6 h up to 48 h. These samples were stored in a refrigerator and analyzed within a week.

Radioimmunoassay for Vincristine. Serum and urine concentrations of vincristine sulfate were determined by a sensitive radioimmunoassay [18]. Vincristine sulfate (NSC 67574), lot no. 67522, kindly provided by Dr. John Douros, National Cancer Institute, Bethesda, Maryland, was used as a standard. Tritium-labeled vinblastine sulfate (specific activity 10.4 Ci/mmol) was obtained from Amersham Corp., Arlington Heights, IL. The unfractionated lyophilized antiserum obtained from rabbits by injection of 4-deacetylvinblastine C-3 carboxazide coupled to bovine serum albumin [14] was generously provided by Dr. Mary Root, Lilly Research Laboratories, Indianapolis, IN. Appropriate dilutions of the blood serum or urine samples were made with glycine buffer (0.2 *M* glycine-HCl, pH 8.8; 0.25% crystalline human albumin, ICN Pharmaceuticals, Inc., Cleveland, Ohio; 1% normal lamb serum, North American Biologicals, Inc., Miami, FL; and 242 mg merthiolate per liter), and concentrations of the alkaloid were determined by radioimmunoassay [18]. Radioactivity from each sample was converted into disintegrations per minute (dpm) from a standard quench curve. From the total amount of input radioactivity, the percent labeled alkaloid bound was calculated after substraction of the nonspecific radioactivity. For these calculations a computer program was set up which converted the raw counts per minute (cpm) data into dpm, took an average of the duplicate values, substracted the background, and calculated the percent bound radioactivity. From the known amount of vincristine sulfate and percent bound radioactivity a standard curve was plotted on a log-logit graph, from which the amount of vincristine sulfate present in each diluted blood sample was determined. Vincristine concentrations closer to 50% competition of binding were taken as final values. A standard curve was obtained with each experiment. The mean ± SD 50% competition level of vincristine sulfate from 30 separate experiments was 0.27 ± 0.082 ng.

Data Analysis. Inspection of the drug concentration-time data plotted on semilogarithmic paper revealed a tri-exponential decay pattern. Initial pharmacokinetic parameter estimates for each patient were obtained by a modified CSTRIP program [17] to yield the apparent volume of the central compartment (V_c) along with the microscopic rate constants. These data were further analyzed through the use of a nonlinear least-square regression program NONLIN [11] in conjunction with a specific subroutine for a two- or three-compartment open model. The three-compartment open model fitted the raw data better than the two-compartment open model in three patients, as judged by Akaike's information criterion [22]. For the three-compartment model, better fit of the data was obtained when raw data points earlier than 5 min were omitted. 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 determined by NONLIN computer program [11]. The biological half-life ($t_{1/2}$) of serum vincristine was calculated

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

$$AUC_0^\infty = \frac{A_1}{\alpha} + \frac{A_2}{\beta} + \frac{A_3}{\gamma}. \quad (2)$$

Plasma clearance was calculated by Eq. 3:

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

Apparent volume of the central compartment (V_c) and the distribution volume at steady state (V_{dss}) [21] were calculated by Eq. 4 and 5:

$$V_c = \text{Dose}/A_1 + A_2 + A_3\,; \quad (4)$$

$$V_{dss} = \text{Dose}\left(\frac{A_1}{\alpha^2} + \frac{A_2}{\beta^2} + \frac{A_3}{\gamma^2}\right)/(AUC_0^\infty)^2. \quad (5)$$

The apparent volume of distribution, V_B [8], was also calculated by Eq. 6, and was normalized to 1.73 m^2 body surface area:

$$V_B = \frac{\text{Dose}}{AUC_0^\infty \times \text{terminal rate constant}}. \quad (6)$$

The fractions of the drug during the terminal phase in the model compartments 1, 2, and 3 were calculated according to Nagashima et al. [12] with the help of a computer program. Body surface area (BSA) was estimated for each subject, where BSA = 0.0235 $H^{0.422} \times W^{0.515}$, where H is height in centimeters and W is the body weight in kilograms [6]. Glomerular filtration rate (GFR) [16] was estimated from the equation:

$$\text{GFR (ml/min per 1.73 m}^2) = \frac{0.55 \times \text{body length (cm)}}{\text{Serum creatinine (mg/100 ml)}}.$$

Results

The computer-fitted and the experimental data for subject 2 are depicted in Fig. 1. The mean half-lives of the three phases of the plasma tri-exponential decay curves, α, β, and γ were, respectively, 2.6 min, 41 min, and 1,531 min (Table 2). The microscopic rate constants, k_{10}, k_{12}, k_{21}, k_{13}, and k_{31} in the three-compartment open model were 0.045 min^{-1}, 0.088 min^{-1}, 0.028 min^{-1}, 0.121 min^{-1}, and 0.0026 min^{-1}, respectively. The apparent volume of the central compartment (V_c) and the volume of distribution at steady state (V_{dss}) were, respectively, 3.25 l and 215.9 l (Table 2). The apparent volume of distribution (V_B) calculated by another method gave slightly different results (Table 2). The plasma clearance of the drug, 146.18 ml/min per 1.73 m^2 BSA, was higher than the average glomerular filtration rate of 97.08 ml/min per 1.73 m^2 (Table 3). Area under the concentration curve from zero to infinity (AUC_0^∞) for 2 mg/m^2 BSA drug dose averaged 27,816 nM · min (Table 3). However, the child whose leukemia was clinically refractory to vincristine (subject 4) had an AUC_0^∞ of 16,380 nM · min, and a plasma clearance of 227.5 ml/min per 1.73 m^2. Urinary excretion of vincristine sulfate from one patient indicated that 36.57% of the total dose was excreted by 90 h, whereas in another patient 24.3% of the drug was excreted by 48 h (Table 4). On closer examination of the urinary excretion data, it was noted that the drug concentration in one patient (BS)

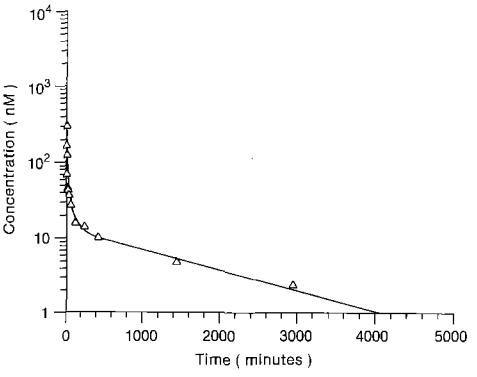

Fig. 1. Pharmacokinetics of vincristine sulfate in the serum of pediatric patient no. 2. △, experimental values; –, computer-fitted data

Table 2. Pharmacokinetic parameters for each patient

Subject no.	Dose mg/m^2	α min^{-1}	β min^{-1}	γ min^{-1}	$\gamma t^1/_2$ min	k_{10} min^{-1}	k_{12} min^{-1}	k_{21} min^{-1}	k_{13} min^{-1}	k_{31} min^{-1}	V_c l	V_c l/1.73 m^2	V_{dss} l/1.73 m^2	V_B
1	1.82	0.330	0.013	0.00027	2,491	0.076	0.097	0.018	0.154	0.0009	0.75	1.69	368	478
2	1.73	0.236	0.016	0.00063	1,094	0.038	0.082	0.026	0.104	0.0025	2.01	3.01	140	185
3	1.31	0.232	0.023	0.00070	1,007	0.022	0.085	0.039	0.106	0.0044	4.44	5.04	139	159
4[a]	2.02		0.033	0.00049	1,414	0.004	0.025	0.004			25.6	55.98	501	464
Mean[b]					1,531	0.045	0.088	0.028	0.121	0.0026		3.25	215	
± SD[b]					833	0.028	0.008	0.011	0.028	0.0018		1.69	132	

[a] Data in this subject better fitted into a two-compartment model
[b] Mean ± SD for subjects 1, 2, and 3

Table 3. Plasma clearance and model independent parameters

Subject no.	Dose mg/m^2	Serum creatinine mg/100 ml	Glomerular filtration rate ml/min per 1.73 m^2	Plasma clearance ml/min per 1.73 m^2	AUC_0^∞ nM · min	AUC_0^∞ (2.0 mg) nM · min
1	1.82	0.5	124.3	129.3	26,386	28,995
2	1.73	0.9	83.78	116.6	27,840	32,184
3	1.31	1.0	89.43	111.3	22,078	33,706
4	2.02	0.7	90.82	227.5	16,544	16,380
Mean			97.08	146.18	23,212	27,816
± SD			18.40	54.74	5,074	7,873

Table 4. Urinary excretion of vincristine sulfate from pediatric patients receiving drug by IV bolus

Time (hs)	Percent total administered drug	
	BS[a]	JL[b]
0–24	12.7	17.5
24–48	13.25	6.8
48–72	6.65	ND[c]
72–90	3.97	ND

[a] Dose 2.0 mg
[b] Dose 1.2 mg
[c] Not determined

was in the range of 10^{-7} M up to 78 h (data not shown). In general, the urine drug concentration was 10- to 50-fold higher than the blood plasma concentration at 24 h.

Discussion

In the three-compartment open model the microscopic rate constants from compartment 1 to compartment 2 and compartment 3 (k_{12} and k_{13}) differ slightly, but the rate constant from compartment 3 to compartment 1 (k_{31}) is 10.7-fold lower than the rate constant from compartment 2 to compartment 1 (k_{21}). The k_{31} is lowest among all the rate constants, and thus could be the rate-limiting step in the elimination of vincristine from the body. The long terminal biological half-life ($\gamma t_{1/2}$) of 25.5 h and the low k_{31} value suggest a strong tissue or cellular binding of the drug and a slow release into blood plasma. Calculation of the fractions of vincristine into various compartments in the model during the terminal elimination phase indicate that a predominant amount (92%) of the drug is in the slowly accessible compartment 3 (data not shown). In compartments 1 and 2, distribution of the drug during the terminal phase is 2% and 6%, respectively. These findings are further corroborated by a large apparent (V_{dss} of 215.9 l), which is 12 times larger than the body fluid (58% of body weight, 17.4 l) from a 30-kg child.

The total area under the drug concentration-time curve (AUC_0^∞) for a 2-mg dose is 27,816 nM · min, 92% of which is contributed by the γ phase of the model. It is noteworthy that the AUC for maximum metaphase arrest of cells [3, 5] and 50% cell kill [9] are well within the range of clinically achievable AUC following IV bolus injection of vincristine. The calculated plasma clearance of vincristine is 146 ml/min per 1.73 m^2, which is slightly higher than the estimated glomerular filtration rate (97 ml/min per 1.73 m^2). It is interesting to note that the leukemic child who was unresponsive to vincristine (subject 4) had a two-fold increase in the plasma clearance and a smaller AUC compared with the other children. Additional data are needed to verify these interesting findings. Urinary excretion data from one patient over a period of 90 h indicate a 36.6% drug elimination, whereas in another patient 24.3% elimination was obtained up to 48 h. With IV bolus injection of ^{3}H-vincristine, 7.8%–26.2% urinary excretion of radioactivity up to 72 h has been obtained in five adult patients [2, 10]. More data are needed to establish the differences, if any, in the drug excretion between adult and pediatric patients.

In conclusion, the long biological half-life, a large volume of distribution, and a low elimination rate constant of vincristine from poorly perfused tissues to the plasma indicate an avid tissue binding and a slow release of the drug from the body. These pharmacokinetic parameters may be related to the pharmacological properties of vincristine.

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