Cancer Chemother. Pharmacol. 2, 243–246 (1979)

Cancer Chemotherapy and Pharmacology

Clinical Pharmacokinetics of Vindesine

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Summary. *The pharmacokinetics of vindesine were investigated in five patients with advanced cancer who were receiving the drug. Following a rapid IV bolus dose, vindesine kinetics were described by a triphasic serum decay curve compatible with a three-compartment open mammillary model. Serum half-lives were 2 min, 50 min, and 24 h for the fast, middle, and slow phases, respectively. The volume of the central compartment approximated the plasma volume in all patients studied. Distribution occurred quickly into a superficial tissue compartment in fairly rapid equilibrium with the plasma compartment, and also into a deep tissue compartment with slower redistribution to the central compartment. The large apparent volume of distribution and long elimination half-live suggest extensive tissue sequestration or delayed excretion of the drug in man. The slightly increased serum half-life of vindesine compared with published results for vinblastine may account for the greater degree and longer duration of marrow suppression seen clinically with vindesine.*

Introduction

Vindesine, or desacetyl vinblastine amide sulfate, is a new semisynthetic vinca alkaloid derivative, which has a wider spectrum of antitumor activity than vinblastine in animal tumor test systems and a toxicity somewhere between that of vincristine and that of vinblastine [13, 15]. The drug is currently the subject of extensive clinical trials throughout the world. Phase I studies demonstrated objective antitumor activity against several hematologic and nonhematologic advanced neoplasms in humans [1, 3, 7, 9, 14]. Phase II studies have confirmed this activity [4, 6, 8, 17], and phase III studies are in progress. In some advanced acute lymphoblastic leukemia patients resistant to vincristine [6, 8, 14] and in some solid-tumor patients resistant to vinblastine [9], vindesine apparently lacks cross-resistance with the two naturally occurring vincas, as it is able to induce remissions in these resistant patients with advanced disease. As with the parent compound vinblastine, the major dose-limiting toxicity for vindesine is myelosuppression. The pharmacokinetics of IV administered vindesine sulfate were investigated in five patients with advanced cancer who were treated with the drug at the Lilly Clinic during the phase I study.

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Materials and Methods

A total of eight separate studies were completed in five patients with advanced cancer not amenable to conventional therapy. Patients were given 1–3 mg vindesine/m^2 by rapid bolus IV injection. Whole blood samples were collected at 0, 5, 10, 20, 30, 45, 60, and 90 min, then at 2, 4, 7, 12, 24, 36, 48, 72, 96, and 120 h after injection. Aliquots of serum were analyzed for vindesine concentration by radioimmunoassay [12].

Results

In all eight studies, serum vindesine concentration followed a well-demarcated triphasic decay with time when the data were plotted semilogarithmically (Fig. 1). After an initial very rapid descent, followed by a somewhat slower decay lasting about 3 h, serum vindesine concentrations were well fitted in all patients by a terminal phase straight line until 96–120 h, at which time the drug was no longer detectable in the serum. Such a triphasic decay may be represented mathematically by an equation with three separate exponentially decaying terms,

$$Cp = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}.$$

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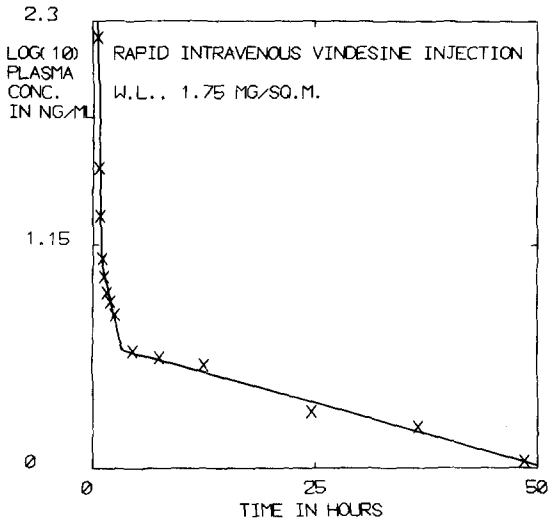

Fig. 1. Semilogarithmic plot of serum vindesine concentrations vs time after injection for one patient, WL

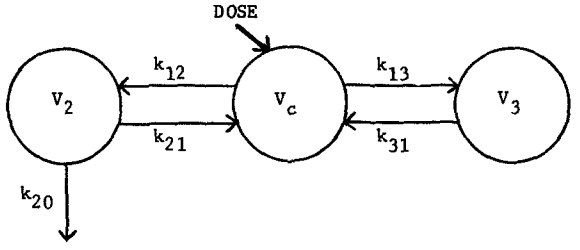

Fig.2. Diagrammatic representation of the three-compartment open mammillary model with elimination from the superficial tissue compartment

VINDESINE KINETIC MODEL

DIFFERENTIAL EQUATIONS:

$$dX_1/dt = -k_{12}X_1 - k_{13}X_1 + k_{21}X_2 + k_{31}X_3$$

$$dX_2/dt = -k_{21}X_2 - k_{20}X_2 + k_{12}X_1$$

$$dX_3/dt = -k_{31}X_3 + k_{13}X_1$$

INITIAL CONDITIONS:

$$X_1(0) = \text{DOSE}; \quad C_1(0) = \text{DOSE}/V_c$$

$$X_2(0) = 0$$

$$X_3(0) = 0$$

Fig. 3. The system of simultaneous linear differential equations and their corresponding initial conditions representing the three-compartment open mammillary model

Table 1. Mean pharmacokinetic parameters for vindesine (8 observations in 5 patients)

Parameter	Mean (±SD)	
$t_{1/2}$ alpha, h	0.038	(0.017)
$t_{1/2}$ beta, h	0.822	(0.273)
$t_{1/2}$ gamma, h	24.33	(11.11)
k_{12}, h^{-1}	11.66	(5.07)
k_{21}, h^{-1}	0.818	(0.471)
k_{13}, h^{-1}	9.31	(4.88)
k_{31}, h^{-1}	0.104	(0.036)
k_{20}, h^{-1}	0.550	(0.216)
V_c, % body weight	5.49	(1.80)
V_2, % body weight	29.3	(19.2)
V_3, % body weight	811	(402)

The simplest pharmacokinetic model compatible with the observed plasma decay pattern is a three-compartment open model. One such model, a three-compartment linear mammillary model, is shown in Fig. 2 and represents the one of the several three-compartment models that we have chosen for analysis of the data. In this model the middle or central compartment is assumed to be in instantaneous equilibrium with the plasma. Since animal studies have indicated that biliary excretion is the major route of elimination [2], the second compartment, V2, is assumed to be in equilibrium with the hepatobiliary system; and elimination occurs principally from the second compartment. In addition there is a third or deep tissue compartment, V3, which is unidentified physiologically.

The set of simultaneous differential equations which describe the aforementioned model [16] is shown in Fig. 3. It is implicit in this set of equations that the rate of transfer of an amount of drug out of any compartment is proportional to the amount remaining in that compartment at any given time – in other words, a first-order process. By means of a nonlinear modeling program called MLAB [5] and with the aid of a DEC-10 digital computer, serum concentration data for each study were fitted simultaneously to the system of equations shown. In all eight cases a reasonably good fit of the data to the model was obtained.

The means and standard deviations of the pharmacokinetic parameters examined for eight studies in five patients are shown in Table 1. The extremely rapid initial decay half-life is only 0.038 h, or about 2 min, followed by a beta-phase half-life of just under 1 h and a terminal elimination half-life of about 24 h. Note that of the five transfer constants shown, k_{12} and k_{13}, i.e., the exit rate constants from the central compartment, are much larger in magnitude than the others, indicating that distribution of vindesine from plasma to tissues is the main reason for the initial rapid plasma clearance. In contrast, k_{20} the elimination

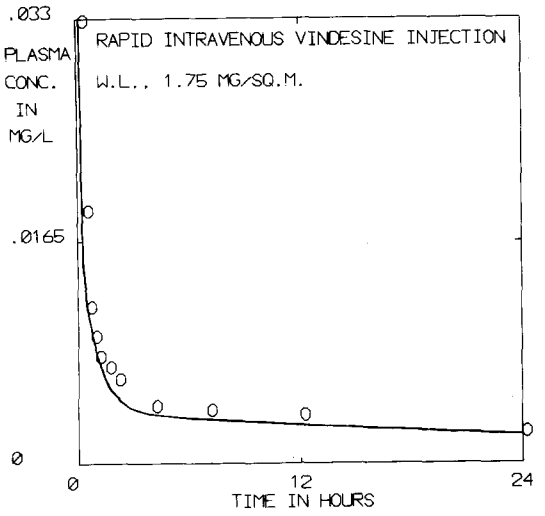

Fig. 4. Linear plot of serum vindesine concentrations vs time after injection for one patient, WL. The open circles represent observed concentrations. The solid line is a model-predicted computer-drawn line obtained by numerical integration of the system of differential equations with fitted kinetic parameters

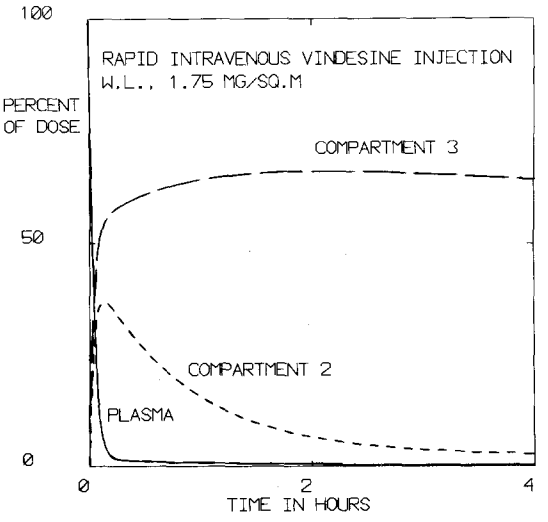

Fig. 5. Model predicted amounts of drug remaining in central, superficial, and deep tissue compartments plotted vs time after injection

rate constant, is less in magnitude; and this explains the much longer elimination half-life. Detailed urinary excretion kinetics were not carried out in most patients due to extraction difficulties, but studies by Owellen et al. [11] suggest low renal clearance of vindesine.

Discussion

The most consistent parameter in the model was the volume of the central compartment, Vc. This comprised about 5.5% of the body weight, which is comparable to plasma volume. The beta-phase volume of distribution was about 30% of the body weight, while the total volume of distribution averaged eight times the body weight, implying extensive binding of the drug in the deep tissue compartment. The deep tissue compartment has not been identified physiologically, but may represent microtubular protein.

In Fig. 4, experimental data points representing plasma vindesine concentrations are plotted as open circles for one patient, WL. The solid line is a computer-drawn curve representing plasma vindesine levels predicted from the model parameters just presented. Good agreement between the experimental data and predicted curve was found for 96 h after the IV dose.

In Fig. 5 the solid line for the predicted plasma curve is again shown, this time plotted as a percentage of the administered dose. The two broken lines shown for compartments 2 and 3 were obtained by direct integration of the set of differential equations and represent the amounts of drug remaining in compartments 2 and 3 respectively, expressed as percentages of the administered dose. As such, they are strictly theoretical curves, do not represent data points, and are obviously model-dependent. It is of note that while the plasma and superficial compartments are essentially in equilibrium after 4 h, the deep tissue compartment, by contrast, rapidly sequesters over 60% of the dose after 15 min and retains it avidly. Near-baseline levels in the third compartment are not reached until 72–96 h. The model thus predicts a very high degree of tissue bioavailability for vindesine. The slightly longer serum half-life of vindesine, compared with published results for vinblastine [10], may account for the greater degree and longer duration of marrow suppression seen clinically with vindesine when equivalent doses of each are given.

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Received September 25, 1978/Accepted March 12, 1979