# Pharmacokinetics of Vindesine and Vincristine in Humans[1]

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## SUMMARY

Vindesine, a new Phase 1 *Vinca* alkaloid congener, exhibited serum pharmacokinetic behavior in humans compatible with a three-compartment, open mammillary model. The kinetic parameters included: $t_{1/2} \ \alpha = 3.24 \pm 1.14$ min, $t_{1/2} \ \beta = 99.0 \pm 44.5$ min, $t_{1/2} \ \gamma = 1213 \pm 493$ min, $V_c \ (V_\alpha) = 4.81 \pm 2.12$ liters, $V_\beta = 58.2 \pm 50.5$ liters, $V_\gamma = 598 \pm 294$ liters. Vincristine, studied only for the first 4 hr, behaved like a two-compartment system, with values of $t_{1/2} \ \alpha = 3.37 \pm 0.72$ min, $t_{1/2} \ \beta = 155 \pm 18$ min, $V_\alpha = 4.53 \pm 0.49$ liters, and $V_\beta = 57.3 \pm 21.1$ liters. Urine excretion data demonstrated that most drug elimination occurred within the first 24 hr and amounted to $13.2 \pm 5.9\%$ for vindesine and $9.5 \pm 5.1\%$ for vincristine.

## INTRODUCTION

VDS[3] (M.W. 851 as sulfate salt) (Chart 1) is a new synthetic derivative of VLB developed by Eli Lilly Research Laboratories, Indianapolis, Ind. (3, 4, 16). This compound has shown good antitumor activity in animals at a level comparable to that of VCR (M.W. 922) as sulfate salt. Although neurotoxicity is difficult to evaluate in animal systems, it was hoped that VDS would have few or no clinical neuropathic effects. Studies of the drug have now completed Phase 1 and will soon be entering Phase 2. Toxicity consisted of hematopoietic depression with decreases in both WBC and platelet counts, some alopecia, and mild neurotoxicity (1, 2, 5). All these effects appear to be dose related. As studies progress to Phase 2, it is hoped that significant antitumor effects will occur without dose-limiting neurotoxicity.

Presumably, like the other *Vinca* alkaloids, VDS kills cells by disrupting microtubular structures since it too binds to tubulin, the subunit protein of microtubules. The affinity of this binding ($K_a$, $3.3 \times 10^6$ liters/mole) has been determined to be very similar to that for both VCR and VLB ($K_a$'s, $8.0 \times 10^6$ and $6.0 \times 10^6$ liters/mole, respectively) (9, 10, 14). In addition, VDS prevents the polymerization of tubulin at a concentration almost identical with that for VLB and VCR (13).

As part of our continuing interest in the pharmacology of the *Vinca* alkaloids and in conjunction with Phase 1 studies

of the drug in The Johns Hopkins Oncology Center, we have investigated the pharmacokinetics of VDS in the serum of patients receiving the drug in pharmacological doses between 1.5 and 4.0 mg/sq m. In addition, VCR levels were monitored in patients receiving routine doses of 0.025 mg/kg. Assay of the drugs was performed with a new radioimmunoassay for the *Vinca* alkaloids, first developed in studies by Nelson et al. (6) and Root et al. (15). Preliminary reports of data on the plasma pharmacokinetics of VDS in humans have appeared. This report is an expansion of our earlier experience (6, 11).

## MATERIALS AND METHODS

**Serum Samples.** After informed consent was obtained, blood samples were collected from patients treated with varying doses of VDS and VCR as part of a Phase 1 study. The samples were collected at selected time intervals into vacuum tubes with no preservative. The serum was separated and stored at $-20°$ until assayed. All patients had normal serum urea nitrogen and bilirubin values and were at least 4 weeks past any prior chemotherapy. No other chemotherapeutic agents were given during administration of VDS or VCR. Patient ages were between 47 and 56 years.

**Radioimmunoassay.** The following reagents were placed in 5-ml polyethylene tubes in this order: 200 $\mu$l of glycine buffer [0.2 M glycine (pH 8.8), 0.25% crystalline human albumin (4 times recrystallized; ICN Pharmaceuticals Inc., Cleveland, Ohio), 1% normal lamb serum (North American Biologicals, Inc., Miami, Fla.), and 242 mg Merthiolate per liter]; 100 $\mu$l of unknown serum or standard solution; 100 $\mu$l [$^3$H]VLB solution ($9 \times 10^{-9}$ or $1.5 \times 10^{-9}$ g/ml); 100 $\mu$l of antiserum (diluted 1:1000 with glycine buffer). The contents of the tubes were mixed gently, and the tubes were capped and incubated for 4 days at $4°$. To each tube were then added 500 $\mu$l of dextran-charcoal suspension [0.5% Norit A (Amend Drug and Chemical Co., Irvington, N.J.) and 0.25% dextran 70 (Pharmacia, Upsala, Sweden) in glycine buffer], and incubation was continued at room temperature for 30 min with occasional gentle shaking. The tubes were centrifuged at $1000 \times g$ for 5 min, and the supernatant was decanted directly into scintillation vials. Instagel (10 ml; Packard Instrument Co., Inc., Downers Grove, Ill.) was added, and the vials were counted in a Packard 300 scintillation spectrophotometer.

Two batches of [$^3$H]VLB, labeled in the aromatic ring portion of the drug, were used. The 1st batch, prepared by us, had a specific activity of 2.484 Ci/mmole, was 85% isotopically pure, and was used at a concentration of $9.0 \times$
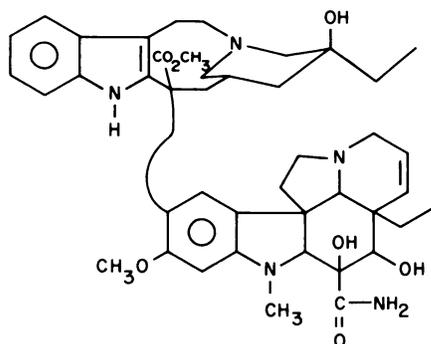
Chart 1. Structure of VDS.

$10^{-9}$ g/ml. The 2nd batch was purchased from Amersham/ Searle Corp., Arlington Heights, Ill., had a specific activity of 8.2 Ci/mmole, was 95% isotopically pure, and was used at a concentration of $1.5 \times 10^{-9}$ g/ml. The [$^3$H]VLB was prepared by exchange with [$^3$H]trifluoroacetic acid and purified by column chromatography on P-11 cellulose phosphate; the purity was checked with 3 thin-layer-chromatography systems (8). No exchangeable $^3$H was in either preparation.

The standard solutions contained isotopically unlabeled VDS (supplied by Eli Lilly Research Laboratories as 10 mg sulfate salt together with 50 mg mannitol in sealed vials) in glycine buffer, with concentrations between 0.2 and 100 × $10^{-9}$ g/ml. The following controls were also run: Control 1, 100 μl of nonimmune rabbit serum substituted for the antiserum; Control 2, 100 μl of glycine buffer in place of standard or unknown.

**Calculations.** The cpm of Control 1 were subtracted from those of Control 2, and the difference was made equal to 100% bound cpm = $A$. The cpm of Control 1 were then subtracted from the cpm of the standard or unknown, and this difference was divided by $A$

$$\text{Control 2} - \text{Control 1} = A$$

$$\frac{\text{Sample} - \text{Control 1}}{A} \times 100 = \% \text{ bound}$$

where the percentage bound for the standard curve was plotted on logit paper, and the unknowns were then read from the linear portion of the graph.

## RESULTS

A standard curve for the radioimmunoassay (Chart 2) was found to be linear between concentrations of 0.1 to 0.3 and 20 to 60 ng/ml. Identical curves were obtained for VCR, for VDS, and for VLB with or without serum. For each set of serum samples used, a separate standard curve was determined, and the unknown samples were analyzed according to that specific standard curve.

The concentration of VDS in each serum sample was calculated and plotted on semilog paper (Chart 3). Different time scales were used, and the $\alpha$, $\beta$, and $\gamma$ phases were easily separated and quite distinct. With the curve feathering technique, all 3 phases were analyzed. Regression analysis gave

$r$ values for each phase that were greater than 0.9, whereas attempts to separate out only 2 phases yielded $r$ values consistently and significantly lower ($<0.9$). The $t_{1/2}$'s and intercepts obtained from these lines are shown in Table 1.

From this analysis the concentration of VDS in the plasma could be expressed by the equation

$$Cp = Ae^{-A_1 t} + Be^{-B_1 t} + Ce^{-C_1 t}. \qquad (A)$$

With these parameters the curve was then analyzed as a 3-compartment open mammillary model (Chart 4). Solution of the necessary equations (17) gave the parameters as listed in Table 1.

From this analysis it appears that the initial ($\alpha$) clearance phase was very fast with a $t_{1/2}$ of a little longer than 3 min, whereas the $\beta$ phase had a $t_{1/2}$ of about 100 min, and the $\gamma$ phase had a $t_{1/2}$ of a little longer than 20 hr. The volume of the control compartment ($V_c$, 4.8 liters) was compatible (as expected) with the total blood volume. The final fictive volume ($V_\gamma$) was very large, about 10 times the total body weight. The elimination constant ($K_{cl}$) was low with a value of $6.04 \times 10^{-3}$ min$^{-1}$.

Analysis of transfer constants revealed that the difference between $K_{\beta c}$ and $K_{\gamma c}$ was significant at the 0.025 level, whereas the difference between $K_{c\beta}$ and $K_{c\gamma}$ was not significant ($p < 0.20$). This supports the use of a 3-phase analysis; $K_{\beta c}$ and $K_{\gamma c}$ were strikingly different, whereas $K_{c\beta}$ and $K_{c\gamma}$ just happened to be close to each other.

Radioimmunoassay determination of VDS in urine was performed for each of 4 patients in a manner identical with that for serum samples (save for the use of higher dilutions) on fractionally collected specimens; the data appear in Table 2. The majority of drug was cleared in the 1st 24 to 36 hr, with only small amounts appearing after this.

Analysis of VCR in serum samples was performed only for the 1st 4 hr after i.v. dosing since with our original [$^3$H]VLB the values after this time were too dilute for measurement.
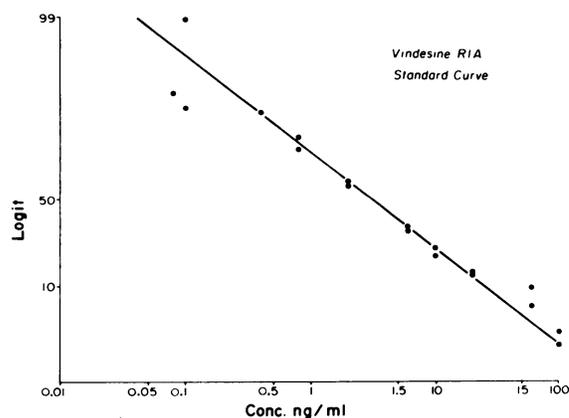


Chart 2. VDS radioimmunoassay (RIA) standard curve. To 200 μl of glycine buffer (see "Materials and Methods") were added 100 μl of standard VLB in 0.9% NaCl solution and 100 μl of antiserum (diluted 1:1000 in glycine buffer). The tubes were held at 4° for 4 days, then 500 μl of dextran-charcoal suspension (see "Materials and Methods") were added and, following a 30-min incubation at room temperature, the charcoal was removed by centrifugation. The supernatant was counted, and the percentage bound was plotted versus concentration (Conc.) on logit paper.

a 2-compartment-model system; the data shown in Table 3 represent an update of our original report (11).

## DISCUSSION

The radioimmunoassay used for these studies is a very sensitive technique for determining low levels of VDS in serum or urine. Cross-reactivity, however, does occur, with standard curves for VCR, VLB, VDS, and DVLB that are all superimposable. Therefore, we cannot be certain when we are determining serum or urine levels that we are measuring only the parent VDS or perhaps a chemically closely related metabolite(s) as well. We shall therefore refer to the activity measured in these biological fluids as if they were unaltered drug. Although this is an admitted simplification, we think it is justified inasmuch as we suspect that any metabolic product formed that would still react in the radioimmunoassay is probably so close to the original that it may have almost equivalent biological activity. An example of this is the VLB metabolite DVLB found in humans (7) that has 50% effective dose values, 50% lethal dose values, and tubulin $K_a$ values very close to those of VLB (10, 13) and, as noted above, reacts in the radioimmunoassay equivalent to the parent.

When VDS was given i.v., there was a rapid fall in serum levels similar to that observed with the closely related drugs

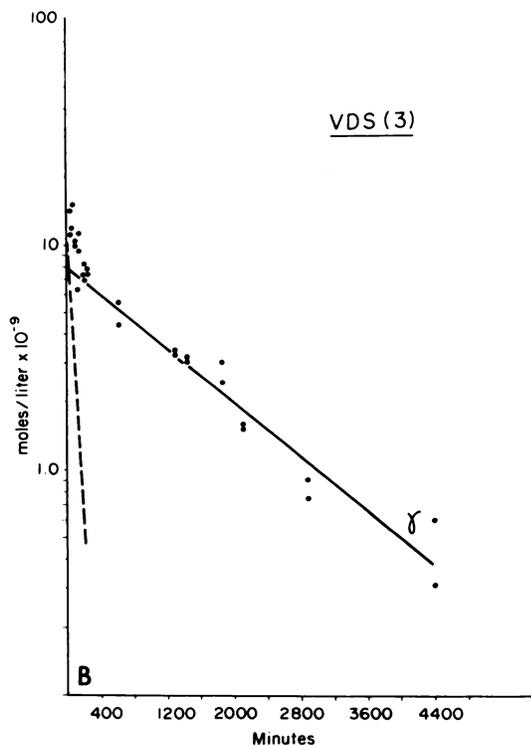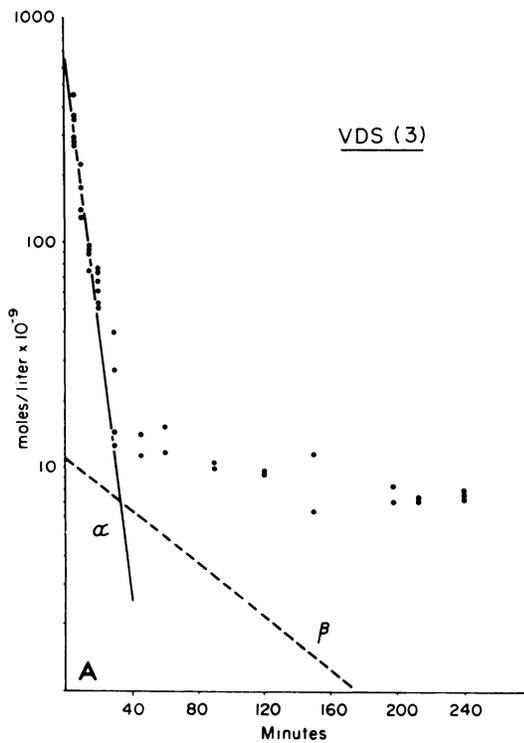Chart 4. Three-compartment open mammillary model.

Chart 3. Serum clearance of VDS as measured by radioimmunoassay. Representative data from 1 patient were obtained by plotting the serum concentration of VDS *versus* time. Chart 3*B* differs from Chart 3*A* in the *abscissa*. Both lines are from the curve stripping process and regression analysis. ———, α phase (*top*) and γ phase (*bottom*); - - - -, β phase.

The data obtained are shown in Chart 5. We realize that a 3rd compartment would be evident only at time points beyond 4 hr and that sampling at longer times would probably demonstrate this. With the present data, however, we used
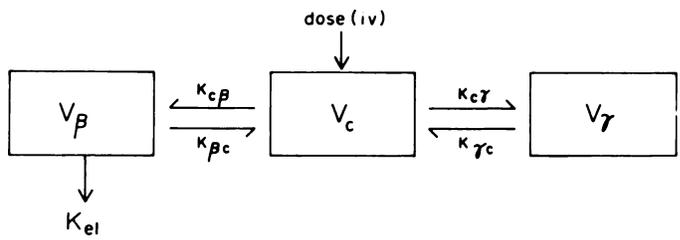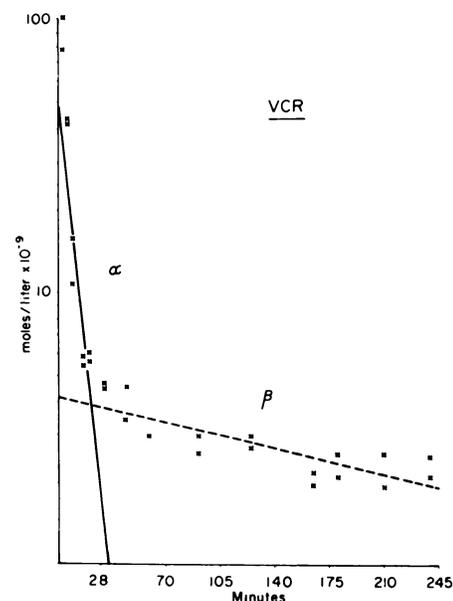
Chart 5. Serum clearance of VCR as measured by radioimmunoassay. Representative data are from 1 patient. Both lines were obtained from the curve stripping process and regression analysis. ———, α phase; - - - -, β phase.

## Table 1
### Three-compartment analysis of VDS serum levels

| Patient | Patient wt (kg) | Total dose (mg) | Dose (mg/sq m) | α phase | | | β phase | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | $t_{1/2}$ (min) | A (×10⁻⁹ mole/liter) | $V_\alpha$ (liters) | $t_{1/2}$ (min) | B (×10⁻⁹ mole/liter) | $V_\beta$ (liters) |
| O. W. | 45 | 2.10 | 1.5 | 4.99 | 653 | 3.69 | 76.8 | 7.52 | 16.1 |
| P. W.-I | 60 | 4.13 | 2.5 | 2.49 | 2190 | 2.18 | 103.4 | 9.08 | 32.5 |
| P. W.-II | | 5.40 | 3.5 | 2.63 | 885 | 7.57 | 95.8 | 8.19 | 87.3 |
| W. L. | 60 | 6.80 | 4.0 | 3.80 | 1270 | 6.25 | 169.5 | 6.36 | 133.0 |
| W. M. | 62 | 6.80 | 4.0 | 2.30 | 1803 | 4.37 | 49.7 | 19.42 | 21.9 |
| Av. | | | | 3.24 ± 1.14 | | 4.81 ± 2.12 | 99.0 ± 44.5 | | 58.2 ± 50.5 |

| Patient | γ phase | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | $t_{1/2}$ (min) | C (×10⁻⁹ mole/liter) | $V_\gamma$ (liters) | C × t (×10⁻⁵) | $K_{el}$ (×10⁻³ min⁻¹) | $k_{c\beta}$ (min⁻¹) | $k_{\beta c}$ (×10⁻³ min⁻¹) | $k_{c\gamma}$ (min⁻¹) | $k_{\gamma c}$ (×10⁻³ min⁻¹) |
| O. W. | 1003 | 7.92 | 210 | 1.70 | 6.68 | 0.063 | 4.09 | 0.073 | 2.05 |
| P. W.-I | 1242 | 7.16 | 391 | 1.97 | 5.40 | 0.148 | 2.57 | 0.128 | 1.30 |
| P. W.-II | 710 | 6.15 | 647 | 0.956 | 5.05 | 0.167 | 5.09 | 0.092 | 2.20 |
| W. L. | 1084 | 3.94 | 851 | 1.47 | 3.53 | 0.126 | 1.57 | 0.055 | 1.07 |
| W. M. | 2025 | 6.42 | 893 | 2.61 | 9.52 | 0.126 | 7.69 | 0.17 | 1.19 |
| Av. | 1213 ± 493 | | 598 ± 294 | | 6.04 ± 2.25 | 0.126 ± 0.039 | 4.20 ± 2.37 | 0.104 ± 0.046 | 1.56 ± 0.52 |

## Table 2
### Excretion of VDS in urine

Urine excreted by patients (listed in Table 1) who were dosed with VDS was measured for VDS content by radioimmunoassay.

| Patient | Cumulative % total dose administered | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 4 hr | 12 hr | 24 hr | 24 hr calculated | 36 hr | 48 hr | 60 hr | 72 hr | 84 hr |
| 1 | 16.5 | | 18.7 | 35.2 | 21.4 | 24.3 | 27.9 | 28.7 | 29.2 |
| 2 | 4.7 | 7.0 | 17.6 | 31.0 | 24.5 | 27.0 | 27.0 | 27.1 | |
| 3 | 3.0 | 4.3 | 6.9 | 38.1 | 7.5 | 7.8 | 7.8 | 7.9 | 8.0 |
| 4 | 5.3 | 7.7 | 9.4 | 22.7 | 10.6 | 11.2 | 11.4 | 11.5 | |
| Av. | | | 13.2 ± 5.9 | 31.8 ± 6.7 | 16.0 ± 8.2 | | | | 19.0 ± 10.8 |

## Table 3
### Pharmacokinetic data obtained by radioimmunoassay of serum samples from 3 patients of the 1st 4 hr after routine pharmacological dosing with 0.025 mg vincristine per kg

| | $t_{1/2}$ (min) | A (×10⁻⁷ mole/liter) | B (×10⁻⁸ mole/liter) | V (liters) |
|---|---|---|---|---|
| α phase | 3.37 ± 0.72 | 3.93 ± 0.84 | | 4.53 ± 0.49 |
| β phase | 155 ± 18 | | 1.01 ± 0.49 | 57.3 ± 21.1 |

## Table 4
### Urine excretion of VCR

VCR in urine samples obtained from patients in Table 3 was analyzed by radioimmunoassay.

| Time (hr) | Cumulative % of total dose |
|---|---|
| 4 | 6.1 ± 3.0 |
| 12 | 8.6 ± 5.2 |
| 24 | 9.6 ± 5.1 |

VLB and VCR (7, 8, 11, 12). This rapid α phase corresponded to distribution of the drug out of the blood volume, represented by the calculated volume of the central compartment ($V_c$), and into the 2nd or β compartment (Chart 4). The calculated volume ($V_\beta = 58L$) seems close to the expected value for the total body water, and thus it is not surprising that elimination occurs from this compartment. The β phase has the greatest variability and degree of uncertainty since it occurs in the break between the other 2 phases and is highly dependent on the values of the background γ phase. That little variation occurs in the α phase reflects the very steep portion of the curve in comparison with the β region, and variations in β and γ then have less effect on the portion of the curve. The final fictive volume ($V_\gamma$) is quite large, indicating extensive tissue binding of the drug. This large $V_\gamma$ together with the very long $t_{1/2}$ for this phase indicates to us that significant amounts of VDS are sequestered in body tissues and are only slowly released and excreted once the initial α and β phases are completed. We would predict from this that not all drug has been cleared from the body after 1 or even 2 weeks, and therefore

with each succeeding dose, following a weekly dose schedule, there is a cumulative effect. This latter may explain why the drugs cause cumulative neurotoxicity. What is not clear, however, is whether this accumulation and/or neurotoxicity results from the original drugs or perhaps from metabolic products, which may or may not cross-react in the radioimmunoassay, as discussed earlier.

Elimination of VDS in the urine in the 1st 24 hr accounted for 13.2% of the total dose administered (Table 2). Calculation of the expected amount eliminated

$$Au = V_\beta K_{el} \int_0^t Be^{-B_1t} + Ce^{-C_1t}\, dt \qquad \text{(B)}$$

predicted a much higher value than this, to the levels also shown in Table 2. Since VLB is eliminated via the bile in humans (7, 12) and VCR is eliminated via this same route in rats (8), we tentatively conclude that the observed discrepancy between the observed urinary excretion and the total predicted elimination represents biliary excretion of VDS in humans. Thus, almost 2.5 times as much VDS would be predicted to be eliminated via the biliary tract than would be eliminated by the urinary route.

Comparing the behavior of VDS and VCR, we see that their pharmacokinetic parameters, at least for $\alpha$ and $\beta$ phases, are parallel (Tables 1 and 3). Urinary excretion of VCR is also very similar to that of VDS; the differences are not statistically significant (compare Tables 2 and 4). We anticipate that examination of VCR samples at longer times will also demonstrate a 3rd phase and that this drug will also behave as a 3-compartment open-model system.

When the data for both VDS and VCR were compared with that for radioactive VLB given i.v. over the 1st 4 hr, the only significant difference appeared in the volume of the $\alpha$ phase ($V_\alpha = 34.6 \pm 6.9L$) (12). However, since VLB is metabolized to DVLB (7), radiolabeled acetic acid is thus released, and the values determined have thereby been affected by these by-products since they were calculated on the basis of total blood radioactivity. We conclude that VLB, VDS, and VCR are similar in their pharmacokinetic behavior, with the probable exhibition by VLB and VCR of a prolonged 3rd phase similar to that found for VDS.

That not all drug is accounted for in the urine suggests that the remainder is either sequestered in the body or eliminated in the bile. Since VCR and VLB are eliminated via the biliary system in rats (8) and humans (7), we strongly suspect that VDS is also excreted via this route. That an appreciable amount of drug is still tissue bound after 72 hr seems probable since serum levels are still measurable. Whether this is original drug or metabolic product we do not know since, as discussed earlier, the radioimmunoassay is known to cross-react with various *Vinca* congeners. With the occurrence at weekly intervals of normal human drug dosing, we anticipate that there is a cumulative effect with VDS, VLB, and VCR and that this may account for the appearance of neuropathy only after multiple drug doses, whereas prolonged although low serum levels afford gradual penetration of drug into nerve tissue.

In summary, VDS pharmacokinetics behave as a 3-compartment, open-model system; the 1st phase is very short, which is compatible with a central compartment equal to the blood volume, whereas the 2nd phase is close to the equivalent of total body water, and the very slow final phase represents extensive tissue binding. Excretion of the drug occurs in the urine, and biliary elimination undoubtedly occurs as well. VCR resembles VDS in these parameters inasmuch as they have been determined for VCR. We expect that there is a cumulative effect for VDS following multiple doses and that delayed neurotoxicity occurring only after several doses is a result of this accumulation, representing gradual penetration of the drug into the central nervous system. As the drug enters Phase 2 studies, we expect that total drug delivery may have to be curtailed by such cumulative neurotoxicity, which is similar to that experienced with VCR.

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