Teniposide (VM26) Disposition in Children with Leukemia

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ABSTRACT

The clinical pharmacokinetics of teniposide (VM-26, NSC 122819) have been studied in 21 children (median age, 4.7 years) with acute lymphocytic leukemia. Teniposide was administered at a dosage of 165 mg/m² as a 30- to 60-min i.v. infusion. Patients were studied either on the first or second dosage of the drug. Plasma samples were assayed for teniposide and metabolites by high-performance liquid chromatography with electrochemical detection. Both compartmental and noncompartmental pharmacokinetic analyses were performed. Systemic clearance and apparent volume of distribution at steady state averaged 13.8 ± 6.0 ml/min/m² (S.D.) and 7.9 ± 4.0 liter/m², respectively. Univariate and multivariate stepwise regression analyses were used to construct mathematical models to describe the relationships between certain patient-specific demographic and laboratory values and the pharmacokinetic parameters, systemic clearance, elimination rate constant, and area under the concentration-time curve. A significant relationship between serum alkaline phosphatase and systemic clearance, elimination rate constant, and area under the concentration-time curve was found, suggesting that liver function influences the disposition of this anticancer drug in humans.

INTRODUCTION

Teniposide (VM26, NSC 122819) is an investigational antineoplastic agent with notable activity in a variety of adult and pediatric cancers (2, 11, 12, 17, 18). Introduced into Phase I clinical trials in the early 1970s, it is a semisynthetic derivative of podophyllotoxin, a potent mitotic inhibitor extracted from the plant Podophyllum peltatum. Although chemically derived from this mitotic inhibitor, teniposide and its structurally related congeners etoposide (VP16) appear to have a mechanism of action different from the parent compound podophyllotoxin (13, 16, 22). We have now analyzed in detail the clinical pharmacokinetics of teniposide in children with acute lymphocytic leukemia.

MATERIALS AND METHODS

Patient Selection. Twenty-one children entered onto the St. Jude Children’s Research Hospital protocol for the treatment of high-risk acute lymphocytic leukemia were studied. Preliminary results of the clinical study have been reported elsewhere (6). Patients eligible for this protocol were previously untreated children with acute lymphocytic leukemia who had one or more of the following clinical features at diagnosis: (a) mediastinal mass; (b) WBC count greater than 100,000/µl; (c) central nervous system leukemia; or (d) E-rosette-positive (T-cell) leukemia cells.

The demographic characteristics of these 21 patients are summarized in Table 1. Informed parental consent was obtained prior to their entry onto this protocol, and all patients were hospitalized for these studies.

Drug Administration and Sample Collection. All patients received an 8-week induction therapy consisting of teniposide and 1-β-arabinofuranosylcytosine given twice weekly during Weeks 1 and 2; prednisone, vincristine, and asparaginase given during Weeks 3 to 6; and a second course of teniposide and cytotoxic ara-cisplatin given twice weekly during weeks 7 and 8. The dosage of teniposide was 165 mg/m² administered as a 30- to 60-min i.v. infusion. Patients were studied either on the first or second dose of the drug. Teniposide was supplied by the National Cancer Institute.

Blood samples (2 to 3 ml) were collected prior to the infusion, at the end of the infusion, and at 0.5, 1, 2, 4, 6, 12, and 24 hr after completion of the infusion, and were immediately placed on ice. The blood was promptly centrifuged, and the plasma was removed and frozen at −70°C until the time of analysis.

Drug Assay. Teniposide and its metabolites were quantitated by a sensitive and specific high-performance liquid chromatography assay which has been described in detail elsewhere (20). In brief, the system uses an isocratic separation of teniposide, cis-picroVM26, and the hydroxy acid metabolite of VM26 using etoposide (VP16) as the internal standard. The mobile phase consists of water/acetonitrile/acetic acid (68/30/2) at a flow rate of 1 ml/min through a reverse-phase 10-µm phenyl column. The column effluent is monitored by UV detection at 280 nm and by electrochemical detection (+0.75-V oxidative potential). The sample preparation used allows quantitation of the parent drug and metabolites in one injection.

Pharmacokinetic Calculations. Pharmacokinetic parameters describing teniposide disposition were calculated from the serial plasma concentration versus time data which were fit to the appropriate multieponential equation using the NONLIN least-squares computer program (15). A weighting factor of 1/y was used for all curve-fitting procedures, and the method of Loo and Riegelman (14) was used to adjust intercept values for the length of the i.v. infusion. The slopes and intercepts of the best-fit line were used to calculate the elimination rate constant (ka), the mircrate constants (k12 and k21), and volume of distribution of the central compartment (Vd.c) using standard compartmental pharmacokinetic equations (10). Noncompartmental systemic clearance (CLss) and volume of distribution at steady state (Vd.w) were calculated using the following:

\[
CL_{ss}(\text{ml/min/m²}) = \frac{\text{Dose (mg/m²)}}{\text{AUC}_{24}(\text{mg/liter-min})}
\]

\[
Vd_{ss}(\text{liter/m²}) = \frac{\text{Cl}_{ss}(\text{ml/min/m²})}{\text{ka} \times \text{Vd}_{ss}(\text{liter/m²})}
\]

where t′ is infusion length.

The area under concentration versus time curve from zero to infinity (AUC∞) and the area-under-the-moment-curve [(C x T) x f] from zero to infinity (AUMC∞) were calculated by the log-trapezoidal and trapezoidal method, respectively.

Statistical Analysis. Simple linear regression analysis was performed to identify significant (p < 0.05) relationships between various pharmacokinetics parameters (ka, Clss, Vd.c, and Vd.w) and patient-specific demographic and biochemical variables. Stepwise multiple regression analysis was performed by standard stepwise selection procedures (7). The

1This work was supported in part by Biomedical Research Grant RR-05584-18, NIH Cancer Center (Core) Grant CA 24176, and NIH Leukemia Program Grant CA 20180, and by American Lebanonese Syrian Associated Charities.

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Received September 7, 1983; accepted November 23, 1983.
function tests in these patients. Nineteen of the 21 patients was 0.36 hr\(^{-1}\). The systemic clearance (C/s) of teniposide in these

tion for a 2-compartment open model. The pharmacokinetic

curve generated from NONLIN estimates of the pharmacokinetic

Table 1

Demographic characteristics of the 21 patients

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height</td>
<td>113.2 ± 29.4 cm*</td>
</tr>
<tr>
<td>Wt</td>
<td>24.2 ± 18.5 kg</td>
</tr>
<tr>
<td>Body surface area</td>
<td>0.86 ± 0.42 sq m</td>
</tr>
<tr>
<td>Age</td>
<td>5.81 ± 4.68 (median, 4.7 yr)</td>
</tr>
<tr>
<td>Sex</td>
<td>7 M, 14 F</td>
</tr>
</tbody>
</table>

Biochemical measurements

- Serum creatinine: 0.61 ± 0.29 mg/dl
- Total protein: 6.46 ± 0.77 g/dl
- Total bilirubin: 3.87 ± 0.55 g/dl
- AP\(^{a}\): 359.3 ± 102.3 IU/liter
- Serum glutamic-pyruvic transaminase\(^{b}\) (ALT): 52.8 ± 88.1 IU/liter
- Serum glutamic-oxaloacetic acid transaminase\(^{a}\) (AST): 92.9 ± 128.8 IU/liter
- Lactic dehydrogenase\(^{b}\): 2031 ± 2666.8 IU/liter

WBC

- Before dose of VM26: 70.2 ± 75.8 × 10\(^{3}\)/µl
- 24 hr after dose of VM26: 23.6 ± 36.2 × 10\(^{3}\)/µl

\(^{a}\) Mean ± S.D.

\(^{b}\) Variables requiring common logarithmic transformation (see text).

value of F was set at 4.0 to enter and at 3.9 to exit for all stepwise

RESULTS

There were 14 boys and 7 girls studied with a median age of 4.7 years. Five patients had diminished renal function [i.e., creatinine clearance estimated to be less than 50 ml/min/sq m]. Only one of these patients had estimated creatinine clearance less than 35 ml/min/sq m. There was a wide range in liver function tests in these patients. Nineteen of the 21 patients studied had increases in one or more of the following tests: AP\(^{a}\) (normal, 475 to 525 IU/liter); lactic dehydrogenase (normal, 30 to 300 IU/liter); ALT (normal, 3 to 35 IU/liter); and AST (normal, 3 to 35 IU/liter). All patients had total bilirubin values within the normal range (0.2 to 1.5 mg/dl). The WBC determined in 21 patients before the first course of teniposide ranged from 1.6 to 183.0 × 10\(^{3}\)/µl (mean, 58.7 ± 62.9 × 10\(^{3}\)/µl; S.D.).

Chart 1 shows the plasma concentration versus time plot of the 21 patients receiving teniposide (165 mg/sq m) as a 30- to 60-min i.v. infusion. The plotted points are the mean of the actual concentrations measured, while the plotted line is the best-fit curve generated from NONLIN estimates of the pharmacokinetic parameters. These data were adequately described by the equation for a 2-compartment open model. The pharmacokinetic parameters for teniposide disposition are summarized in Table 2. The mean terminal half-life (t\(_{1/2}\)) was 8.95 hr. The elimination rate constant (k\(_e\)) represents the sum of all elimination processes including metabolism, biliary, and urinary excretion, was 0.36 hr\(^{-1}\). The systemic clearance (C/s) of teniposide in these

The abbreviations used are: AP, alkaline phosphatase; AUC, area under concentration versus time curve; AST, aspartate aminotransferase or glutamic-oxaloacetic acid transaminase (SGOT); ALT, glutamic-pyruvic transaminase (SGPT).

Table 2

Pharmacokinetic parameters for teniposide disposition

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>1.29 ± 0.77 hr(^{-1})</td>
</tr>
<tr>
<td>t(_{1/2})α</td>
<td>0.86 ± 0.64 hr</td>
</tr>
<tr>
<td>β</td>
<td>0.996 ± 0.036 hr(^{-1})</td>
</tr>
<tr>
<td>t(_{1/2})β</td>
<td>8.95 ± 3.73 hr</td>
</tr>
<tr>
<td>K(_{a})</td>
<td>0.68 ± 0.53 hr(^{-1})</td>
</tr>
<tr>
<td>K(_{e})</td>
<td>0.34 ± 0.17 hr(^{-1})</td>
</tr>
<tr>
<td>k(_{e})</td>
<td>0.36 ± 0.18 hr(^{-1})</td>
</tr>
<tr>
<td>AUC</td>
<td>260.8 ± 187.2 mg/liter·hr</td>
</tr>
<tr>
<td>C(_{l})</td>
<td>13.8 ± 6.9 ml/min/sq m</td>
</tr>
<tr>
<td>Vd(_{ss})</td>
<td>7.9 ± 4.9 liter/sq m</td>
</tr>
<tr>
<td>V(_c)</td>
<td>3.13 ± 2.9 liter/sq m</td>
</tr>
</tbody>
</table>

\(^{a}\) Mean ± S.D.

Table 3

Variables used in univariate and multiple stepwise regression analysis

<table>
<thead>
<tr>
<th>Pharmcokinetic</th>
<th>Demographic-biochemical</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(_{l}) (ml/min/sq m)</td>
<td>Age (yr)</td>
</tr>
<tr>
<td>AUC (mg/liter·hr)</td>
<td>Body surface area (sq m)</td>
</tr>
<tr>
<td>log(AUC)</td>
<td>Height (cm)</td>
</tr>
<tr>
<td>k(_{e}) (hr(^{-1}))</td>
<td>Wt (kg)</td>
</tr>
<tr>
<td>Vd(_{ss}) (liter/sq m)</td>
<td>Serum dehydrogenase (IU/liter)</td>
</tr>
<tr>
<td>V(_c) (liter/sq m)</td>
<td>Blood urea nitrogen (mg/dl)</td>
</tr>
<tr>
<td>log(V(_c))</td>
<td>Total protein (g/dl)</td>
</tr>
</tbody>
</table>

children ranged from 4 to 22 ml/min/sq m (mean, 13.8 ± 6.0).

Table 3 lists the dependent and independent variables used in the regression analysis. Biochemical variables requiring common logarithmic transformations were albumin, total bilirubin, alkaline phosphatase (AP), serum glutamic pyruvic transaminase (ALT), serum glutamic oxaloacetic acid transaminase (AST), and lactic dehydrogenase. Pharmacokinetic variables that were transformed included AUC and V\(_c\). The variables correlated (correlation coefficient, r > 0.40) in a univariate analysis with C\(_{l}\) were log(AP) and log(ALT); log AUC was correlated with log(AP), log (AST) and log (ALT); and k\(_{e}\) was correlated in a univariate analysis with log(AP).

A stepwise multiple regression analysis using the independent variables listed in Table 3 was used to construct a model to describe the variability observed in the pharmacokinetic parameters of C\(_{l}\), k\(_{e}\), log(AUC), and Vd\(_{ss}\). This analysis revealed that only the log(AP) was a significant predictor in a linear model for C\(_{l}\), k\(_{e}\), and log(AUC), yielding the following:
The analysis of VdM (liters/sq m) revealed that only weight contributed significantly to the stepwise regression, but explained only 17% of the observed variability. The change (decrease) in WBC (lymphoblasts) from the first teniposide dose to contribed significantly to the stepwise regression, but ex

who received 165 mg/sq m) as a 30- to 145-min i.v. infusion (9,

few have used a sensitive and specific high-performance liquid clinical pharmacokinetics of teniposide in adults (1,3,4,19), but

analysis. In 5 patients who satisfied the above criteria, there was a relationship between the decrease in peripheral lymphoblasts over 24 hr and the log(AUC), such that those patients with a higher log(AUC) (relatively more exposure) had a greater decrease in peripheral blast count ($p = <0.05$; $r^2 = 44.5\%$).

**DISCUSSION**

There have been a number of published reports describing the clinical pharmacokinetics of teniposide in adults (1, 3, 4, 19), but few have used a sensitive and specific high-performance liquid chromatography assay (3, 19). Sessa et al. (19) studied 7 ovarian cancer patients receiving 100 to 150 mg/sq m of teniposide over 1 hr as an i.v. infusion. The systemic clearances they observed ranged from 8 to 25 ml/min/sq m, which is in agreement with the results of this study. We have previously described the pharmacokinetics of teniposide in 6 children with acute leukemia who received 165 mg/sq m as a 30- to 145-min i.v. infusion (9, 21). The adequate description of teniposide by a 2-compartment model in our preliminary report, as well as the present study, differs from previously published reports in adults where a 3-compartment model was used (1, 4). This may have been due to differences in the length of i.v. infusion, sampling times, number of samples collected, or analytical methodology. In the current study of 21 patients, the mean values of $t_{1/2\alpha}$ and $t_{1/2\beta}$ are similar to our previously reported values. However, the mean systemic clearance in the present study is higher than we reported previously ($13.8$ versus $8.2$ ml/min/sq m). Reanalysis of the 6 patients from our initial report, in light of the results of this study, show that 3 of the 6 patients in the previous study had elevated values for AP which may have resulted in a lower mean systemic clearance.

The relationship between serum AP and systemic clearance, AUC, and $k_u$ for teniposide, strongly suggest that teniposide disposition in humans is influenced by liver function. In rats, teniposide is excreted predominantly via the bile; however, in humans, fecal recovery of $[^{14}C]$teniposide has been less than 10% (3). Creaven and Allen (4) report that 86% of teniposide is metabolized, which agrees with the fraction of the administered dose recovered in the urine in 72 hr as unchanged drug (16 to 20%). However, this markedly overestimates the percentage of administered drug recovered as metabolite (32%).

AP is sensitive to partial or mild degrees of biliary obstruction, either extra- or intrahepatic. Thus, under such circumstances, the AP may be elevated with a normal serum bilirubin. With hepaticocellular damage, there is little, if any, rise in serum AP; but even with temporary intrahepatic obstruction, AP may increase and, as the obstruction resolves, it promptly returns to normal. Thus, the observation of a relationship between serum AP and teniposide pharmacokinetics has a biological basis. AP

is produced in both the liver and bone, although none of the patients in our study had evidence of bony disease which might account for elevations in AP. Prepubertal children often have physiologically high AP activity; however, we did not find a significant relationship between age and AP or age and systemic clearance when tested in a univariate analysis. Moreover, these patients also had elevations in other hepatic function indicators (ALT, AST, and lactate dehydrogenase) in addition to the AP.

Although the number of patients available for assessing the pharmacodynamic effect of teniposide ($\Delta$WBC) was small, a statistically significant relationship between the teniposide AUC in plasma and in the decrease in circulating lymphoblasts was observed.

In summary, the present study has elucidated the clinical pharmacokinetics of teniposide in pediatric patients with acute leukemia. A relationship between serum AP and $\text{Cl}_u$, $k_u$, and AUC has been shown, although not sufficiently predictive to yield precise dosage guidelines based on hepatic function studies at this time.

**REFERENCES**


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