Pharmacokinetics of Etoposide in Patients with Abnormal Renal and Hepatic Function

Maurizio D'Incalci, Cosmo Rossi, Massimo Zucchetti, Renato Urso, Franco Cavalli, Costantino Mangioni, Yvonne Willems, and Cristina Sessa


ABSTRACT

Etoposide (VP16) pharmacokinetics was investigated in three groups of cancer patients: a control group of 18 patients with normal renal and hepatic function tests in the normal range; a group of 8 patients with normal renal insufficiency; and a group of 15 patients with abnormal hepatic function.

In the control group plasma clearance (Clp), volume of distribution (Vd), and elimination half-life (t1/2) of VP16 were, respectively, 22.8 ± 1.0 (SE) ml/min/m², 11.4 ± 0.8 liters/m², and 5.6 ± 0.4 h.

In patients with renal insufficiency Clp was 12.8 ± 1.1 ml/min/m², Vd was 20.8 ± 4.9 liters/m², and t1/2 was 19.2 ± 4.7 h. A statistically significant correlation (P = 0.0000001) was found between VP16 Clp and creatinine clearance.

In 12 of 15 patients with abnormal liver tests Clp, Vd, and t1/2 were, respectively, 27.9 ± 2.7 ml/min/m², 12.4 ± 1.5 liters/m², and 5.4 ± 0.6 h and are thus similar to those of the control group. In the other three cases with abnormal liver function VP16 plasma levels were very low. In these cases VP16 t1/2 values were similar (5.1, 4.4, and 5.1 h) whereas Clp values (320, 87, and 96 ml/min/m²) and Vd values (142, 33, and 42 liters/m²) were much larger than in controls.

These results suggest that VP16 doses should be reduced in patients with renal function impairment but not necessarily in patients with liver impairment. The high VP16 Clp and Vd values found in a subset of patients with liver impairment require further elucidation.

INTRODUCTION

VP16 is a semisynthetic epipodophyllotoxin derivative widely used in cancer chemotherapy. It is very effective in the therapy of various forms of human malignant tumors including testicular and small cell lung cancer, lymphoma, leukemia, central nervous system tumors, and Kaposi's sarcoma associated with the acquired immunodeficiency syndrome (2). Using specific high performance liquid chromatography (3–7), several pharmacokinetic studies have been made in recent years both in animals (8, 9) and in cancer patients (6, 10–14), but no information was available on whether VP16 doses should be reduced and to what extent in patients with renal or hepatic insufficiency.

This question is clinically relevant since cancer patients commonly suffer from renal or hepatic insufficiency due either to the neoplastic disease itself or nephrotoxic or hepatotoxic treatments or to other concomitant diseases.

In this study we compared VP16 pharmacokinetics in patients with abnormal renal or hepatic function and in a control group of patients with normal kidney and liver function.

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1 This work was supported by the Italian Association for Cancer Research. Presented in part at the 76th Annual Meeting of the American Association for Cancer Research (1).
2 To whom requests for reprints should be addressed, at the Istituto di Ricerche Farmacologiche "Mario Negri, " Via Eritrea 62, 20157 Milan, Italy.
3 The abbreviations used were: VP16, etoposide; DDP, cis-platinum diammine-dichloride.

MATERIALS AND METHODS

Three groups of patients entered this study; their main characteristics and details of previous chemotherapy are set out in Tables 1 to 3.

The first group was composed of 18 cancer patients with normal renal (serum creatinine, 0.6–1.2 mg/100 ml; creatinine clearance, >60 ml/min) and hepatic function (alkaline phosphatase, 60–170 units/liter; serum glutamic-0xaloacetic transaminase, <15 units/liter; γ-glutamyltransferase, 0–28 units/liter; serum glutamic-pyruvic transaminase, <17 units/liter; serum lactate dehydrogenase, 100–225 units/liter, and total bilirubin, <1.2 mg/100 ml).

A second group contained 8 cancer patients with normal hepatic function but renal insufficiency (as defined by a serum creatinine value of >1.5 mg/100 ml and creatinine clearance of <60 ml/min). Patients 19, 20, 21, 24, and 26 had renal insufficiency due to previous treatment with DDP.

A third group contained 15 cancer patients with normal hepatic function but abnormal hepatic tests (total bilirubin, >1.2 mg/100 ml; γ-glutamyltransferase >28 units/liter, and alkaline phosphatase, >170 units/liter).

Many of these patients were receiving concomitant therapy: actinomycin D plus methotrexate (patients 3, 5, 6, and 7); continuous infusion (days 1–5) of bleomycin and s.c. injection (days 4–5) of 1.β-D-α-arabinofuranosylcytosine (patients 11 to 14); patient 17 received DDP and patient 18 received DDP plus mitomycin C. None of the patients investigated had ascites.

Drug Treatment. VP16 for clinical use was supplied by Bristol Myers, New York, NY, as ampuls containing 100 mg in 5 ml for i.v. infusion. The VP16 dose was diluted in normal saline solution, 250 ml/100 mg drug, and administered as a 60-min infusion.

VP16 was given to patients with renal or hepatic dysfunction at daily doses ranging from 70 to 150 mg/m² as a 1-day (patients 24, 25, 26, 28, 30, 32, 33, 34, 36, 37, 38, and 40) or a 3-day course (patients 24, 25, 26, 28, 30, 32, 33, 34, 36, 37, 38, and 40) or a 3-day course (patients 19, 20, 21, 22, 23, 27, 29, 31, 35, 39, and 41). Control group patients were given daily doses of 80–150 mg/m² for 1 day (13 patients) or 5 consecutive days (5 patients) according to the different schedules used. Intervals of 24 h were scheduled between the end of one infusion and the start of the next.

Sample Collection. At various times during and after the first VP16 infusion 5-ml blood samples were taken via an indwelling cannula from the arm not receiving the i.v. infusion, immediately put into heparinized tubes, and spun down at 2000 rpm. In general, samples were taken just before, 15 and 30 min from the start of infusion, at the end of the infusion, and 1, 2, 4, 6, 24, 48, 72, 108, 144, and 172 min postinfusion. Aliquots of the 24-h urines were stored at −20°C until analyzed.

After the last infusion and when the drug was administered as a 1-day course, 5-ml blood samples were also taken 36, 48, 60, and 72 h from the end of the infusion. Urine fractions were collected every 24 h up to 72 h from the end of the last infusion.

Drug Assay. The method described in detail elsewhere (6) can be summarized as follows. Teniposide as internal standard was added to 1 ml of plasma (100 μl of a 100-μg/ml solution). Extraction was carried out with 8 ml of chloroform. After 20 min shaking at room temperature samples were centrifuged at 3000 rpm for 20 min. The organic phase was dried under vacuum and then redissolved with 100 μl of methanol; 10–20 μl of this solution were injected into a Waters Model 6000 A high performance liquid chromatograph equipped with a 254 nm absorption detector. Separation was achieved using an isocratic solvent system of water (64%), acetonitrile (35%), and acetic acid (1%) at a
flow rate of 1 ml/min using a 25-cm-long μBondapak phenyl column purchased from Waters Associates, New York, NY. The sensitivity of this assay was 0.2 μg/ml VP16.

For the VP16 glucuronidation determination, 0.5 ml of urine was incubated for 24 h at 37°C with 0.5 ml of 0.1 M acetate buffer (pH 4.5) and 50 μl (corresponding to 250 milliunits) of β-glucuronidase (from Escherichia coli Kl2; Boehringer Biochemia Robin, Milan, Italy). After incubation the urine was extracted in the same way as plasma. The amounts of VP16 were compared with those found in control samples not treated with β-glucuronidase.

Pharmacokinetic Analysis. Assuming that plasma concentration-time data for each subject can be described by the following model after i.v. bolus

\[ C(t) = \frac{(D/V) e^{-\alpha t} + C e^{-\beta t}}{\alpha} \]

where \( V \) is the volume of the central compartment, \( \alpha \) and \( \beta \) are the complex constants (15), \( C_1 \), \( C_2 \) are dimensionless (\( C_1 + C_2 = 1 \)), \( C(t) \) is the plasma concentration, and \( D \) is the injected dose, then concentration-time data after a 0 order infusion can be described by (16)

\[ C(t) = \frac{(D/V) e^{-\alpha t} + (D/\beta) e^{-\beta t}}{\alpha + \beta} \]

RESULTS

Fig. 1 gives an example of the plasma kinetics of VP16 in five cancer patients with normal renal and hepatic function. No drug accumulation was observed in patients who received five consecutive daily doses, and levels after the first and fifth infusions being similar. Table 4 sets out the pharmacokinetic parameters of VP16 in 18 patients with normal hepatic and renal function. Median values of \( C_{np} \), \( V \), and \( t_\beta \) were 22.0 (range, 17.4–34.6) ml/min/m², 10.9 (range, 6.4–17.8) liters/m², and 5.4 (range, 2.1–9.4) h. \( V_{da} \) mean value was 8.40 ± 0.47 (SE) liters/m², median value was 8.2 (range, 5.0–12.3) liters/m². Urinary excretion of VP16 averaged 40.8 ± 4.2% of the dose, and urinary excretion of VP16 plus VP16 glucuronide was 49.2 ± 2.9%.

Fig. 2A shows plasma VP16 kinetics in patients with renal insufficiency. In the three patients given a single VP16 dose VP16 could be determined at longer times from the end of infusion (Fig. 2B). At 48 h VP16 levels in plasma were 0.59, 0.56, and 0.42 μg/ml, whereas in patients with normal renal function VP16 was never detectable at this interval (i.e., levels were below 0.2 μg/ml).

Table 5 sets out the pharmacokinetic parameters and urinary excretion of VP16 and VP16 plus VP16 glucuronide. Median values of \( C_{np} \), \( V \), and \( t_\beta \) were, respectively, 11.6 (range, 9.1–16.9) ml/min/m², 15.6 (range, 6.3–48.3) liters/m², and 14.6 (range, 8.0–45.0) h. \( V_{da} \) was 12.6 ± 1.5 liters/m², median value was 11.7 (range, 5.6–18.5) liters/m². Urinary excretion of VP16 ranged between 22.2 and 23% of the dose and the total amount of VP16 plus VP16 glucuronide ranged between 5.8 and 30.5% of the dose. The pharmacokinetic parameters in these patients were significantly different from those in the 18 patients with normal renal and hepatic function as assessed by both parametric and nonparametric tests; i.e., \( C_{np} \) was significantly lower.
**VP16 KINETICS IN RENAL AND HEPATIC DYSFUNCTION**

Table 3  Characteristics of patients with hepatic insufficiency

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Disease</th>
<th>Previous chemotherapy</th>
<th>γ-GT* (units/liter)</th>
<th>Alkaline phosphatase (units/liter)</th>
<th>Bilirubin (mg/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>70</td>
<td>F</td>
<td>Gastric adenocarcinomaa</td>
<td>CCNU³ + 5-FU</td>
<td>860</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>64</td>
<td>M</td>
<td>SCLC</td>
<td></td>
<td>208</td>
<td>340</td>
<td>1.6</td>
</tr>
<tr>
<td>29</td>
<td>54</td>
<td>F</td>
<td>Lung adenocarcinoma</td>
<td></td>
<td>475</td>
<td>730</td>
<td>0.7</td>
</tr>
<tr>
<td>30</td>
<td>83</td>
<td>F</td>
<td>Pancreatic adenocarcinoma</td>
<td></td>
<td>840</td>
<td>308</td>
<td>1.5</td>
</tr>
<tr>
<td>31</td>
<td>62</td>
<td>F</td>
<td>Hepatocarcinoma cirrhosis</td>
<td>CCY + VCR + PCZ + PDN</td>
<td>170</td>
<td>308</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>65</td>
<td>F</td>
<td>Hepatocarcinoma cirrhosis</td>
<td>VP16</td>
<td>148</td>
<td>364</td>
<td>3.0</td>
</tr>
<tr>
<td>33</td>
<td>53</td>
<td>M</td>
<td>SCLC³</td>
<td>ADM + VP16 + VCR; DDP + VP16</td>
<td>620</td>
<td>588</td>
<td>6.5</td>
</tr>
<tr>
<td>34</td>
<td>53</td>
<td>F</td>
<td>Gastric adenocarcinoma</td>
<td>ADM + MMC + 5-FU; DDP</td>
<td>260</td>
<td>1200</td>
<td>3.5</td>
</tr>
<tr>
<td>35</td>
<td>53</td>
<td>F</td>
<td>Lunga carcinoma</td>
<td>4-DMDR</td>
<td>423</td>
<td>671</td>
<td>0.8</td>
</tr>
<tr>
<td>36</td>
<td>64</td>
<td>M</td>
<td>Hepatocarcinoma</td>
<td></td>
<td>201</td>
<td>233</td>
<td>32.0</td>
</tr>
<tr>
<td>37</td>
<td>53</td>
<td>M</td>
<td>Hepatocarcinoma</td>
<td></td>
<td>96</td>
<td>580</td>
<td>10.0</td>
</tr>
<tr>
<td>38</td>
<td>72</td>
<td>F</td>
<td>Choledochoadenocarcinoma</td>
<td>VP16 + HU; 5-FU + VCR + STZ + MeCCNU</td>
<td>150</td>
<td>386</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>57</td>
<td>M</td>
<td>Intestinala adenocarcinoma</td>
<td>VP16 + ADM + MMC</td>
<td>220</td>
<td>510</td>
<td>10.5</td>
</tr>
<tr>
<td>40</td>
<td>75</td>
<td>M</td>
<td>Gastric adenocarcinomaa</td>
<td>5-FU + HU; 5-FU + VCR + STZ + MeCCNU</td>
<td>148</td>
<td>855</td>
<td>0.5</td>
</tr>
<tr>
<td>41</td>
<td>71</td>
<td>M</td>
<td>SCLC³</td>
<td>CY</td>
<td>468</td>
<td>462</td>
<td>25.0</td>
</tr>
</tbody>
</table>

a Patients with liver metastases.
³ CCNU, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; 5-FU, 5-fluorouracil; CY, cyclophosphamide; PCZ, procarbazine; PDN, prednisolone; ADM, Adriamycin; VCR, vincristine; MMC, mitomycin C; 4-DMDR, 4-demethoxydaunorubicin; HU, hydroxyurea; STZ, streptozocin; MeCCNU, 1-(2-chloroethyl)-3-(trans-4-methylcyclohexyl)-1-nitrosourea; SCLC, small cell lung carcinoma.

Fig. 1. VP16 plasma levels after the first (left) and fifth (right) daily 1-h infusions of 100 mg/m² in five patients with normal renal and hepatic function.

Table 4  Mean pharmacokinetic parameters and urinary excretion of VP16 in 18 cancer patients with normal renal and hepatic function

<table>
<thead>
<tr>
<th>Dose (mg/m² range)</th>
<th>C₅₀ (ml/ min/m²)</th>
<th>V₅₀ (liters/m²)</th>
<th>t₀ β (h)</th>
<th>VP16 + urinary excretion (% of the dose) of VP16 conjugate</th>
<th>Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>80–120</td>
<td>22.8 ± 1.0⁴</td>
<td>11.4 ± 0.8</td>
<td>5.6 ± 0.4</td>
<td>21–56</td>
<td>39–59</td>
</tr>
</tbody>
</table>

Urinary excretion of VP16 was determined in 10 of these 18 patients. Mean ± SE.

(P < 0.01) whereas V₅₀ and t₀ β were higher (P < 0.01). Fig. 3 illustrates the very good correlation between VP16 C₅₀ and creatinine clearance (P = 0.0000001). Fig. 4 shows plasma VP16 kinetics in patients with abnormal liver function who received drug doses between 80 and 150 mg/m². Plasma levels appeared to vary more in this group. In the majority, plasma levels were comparable to those in the control group. In addition VP16 plasma levels were similar after the first and the third daily infusions. Patients 39, 41 (Fig. 4A), and 40 (Fig. 4B) showed very low VP16 plasma levels. In two of them (patients...
Table 5  Pharmacokinetic parameters and urinary elimination of VP16 in 8 cancer patients with abnormal renal function

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose (mg/m²)</th>
<th>Cₚ (ml/min/m²)</th>
<th>Vₚ (liters/m²)</th>
<th>t₀β (h)</th>
<th>Urinary excretion (% of the dose) of VP16 conjugate</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>100 × 3</td>
<td>9.1</td>
<td>5.5</td>
<td>8.0</td>
<td>16.1</td>
</tr>
<tr>
<td>20</td>
<td>120 × 3</td>
<td>15.6</td>
<td>10.2</td>
<td>9.0</td>
<td>18.8</td>
</tr>
<tr>
<td>21</td>
<td>100 × 3</td>
<td>16.9</td>
<td>12.4</td>
<td>16.1</td>
<td>18.6</td>
</tr>
<tr>
<td>22</td>
<td>80 × 3</td>
<td>12.4</td>
<td>18.2</td>
<td>45.0</td>
<td>23.0</td>
</tr>
<tr>
<td>23</td>
<td>70 × 3</td>
<td>10.9</td>
<td>18.5</td>
<td>35.5</td>
<td>13.6</td>
</tr>
<tr>
<td>24</td>
<td>120 × 1</td>
<td>16.7</td>
<td>14.1</td>
<td>10.6</td>
<td>14.9</td>
</tr>
<tr>
<td>25</td>
<td>120 × 1</td>
<td>10.9</td>
<td>10.9</td>
<td>16.7</td>
<td>14.9</td>
</tr>
<tr>
<td>26</td>
<td>80 × 1</td>
<td>10.2</td>
<td>10.9</td>
<td>13.2</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Mean ± SE 12.8 ± 1.1 20.8 ± 4.9 19.2 ± 4.7

* x3, in 3 doses; x1, in one dose; —, not determined.

Fig. 3. Relationship between VP16 Cₚ and creatinine clearance as assessed by linear regression analysis (r = 0.86; P = 0.000000105).

39 and 41) plasma levels determined again after the third daily infusion were again very low. Fig. 4B shows the pattern in patients given only one dose.

The pharmacokinetic parameters and urinary excretion of VP16 and VP16 plus VP16 glucuronide found in those patients with abnormal hepatic function are shown in Table 6. Cases 39, 40, and 41 are presented separately because they appeared very different from the other 12 cases. In these 12 cases the values were not statistically different from those found in patients with normal and renal hepatic function. Patients 39, 40, and 41 had comparable t₀β values but much larger Cₚ and Vₚ values. The median values of Cₚ, Vₚ, and t₀β in all 15 cases with abnormal liver function were 27.5 (range, 20.1–320) ml/min/m², 12.2 (range, 6.8–142) liters/m², and 4.9 (range, 2.8–9.7) h.

**DISCUSSION**

In the present study VP16 Cₚ was significantly lowered and t₀β was significantly raised in patients with renal insufficiency; excretion of VP16 is in fact much less in these patients than in cancer patients with normal renal function. On the basis of these data it is reasonable to assume that if the VP16 doses and schedules used in patients with normal kidney function are given to patients with renal impairment there is a risk of severe toxicity. The dose-limiting toxicity of VP16 is leukopenia, with a nadir of WBC occurring approximately 10 days after VP16 therapy (24, 25). Since most patients investigated in this study received or had received other leukopenic drugs, it was impossible to determine the relationship between VP16 levels and bone marrow toxicity. However, a relationship between VP16 dose or levels and toxicity has already been established in many studies (13, 24–28) and a high risk of toxicity is to be expected if the drug is cleared at a lower rate from the body.

A good correlation was found between VP16 Cₚ and creatinine clearance, thus suggesting that the doses might be adjusted in relation to creatinine clearance values. It is worth noting that, differently from Cₚ, the increase in the half-life does not correlate with the degree of renal insufficiency. For example patients 25 and 26 with creatinine clearances of 10 and 4 ml/min had considerably shorter VP16 half-lives than patients 22 and 23 who had creatinine clearances of 28 and 27 ml/min. The lack of correlation may be due to the fact that the half-life is a complex parameter reflecting both the elimination and the distribution of the drug (29). In patients with abnormal liver function VP16 Cₚ and t₀β were unaffected. These results are...
drug in the liver, possibly because of reduced active efflux of VP16 from hepatocytes.

Although the finding of low plasma VP16 levels in a subset of patients has still to be elucidated and requires further studies with reference to its possible clinical implications (e.g., hepatotoxicity), considering that VP16 CL was not lower than in patients with normal hepatic function we believe there is no basis for recommending necessarily a VP16 dose reduction in patients with liver impairment. This point is now being checked further in this laboratory using higher VP16 doses.

REFERENCES


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