Pharmacokinetics of High-Dose Etoposide (VP-16-213) Administered to Cancer Patients

Kenneth R. Hande, Peter J. Wedlund, Richard M. Noone, Grant R. Wilkinson, F. Anthony Greco, and Steven N. Wolff


ABSTRACT

Plasma, urine, and cerebrospinal fluid etoposide concentrations have been measured in 12 adult patients after administration of high-dose (400 to 800 mg/sq m) etoposide in order to determine the pharmacokinetics of this drug at these elevated dosages. Increasing the drug dosage produced proportionally higher peak plasma etoposide concentrations (27 to 114 µg/ml) and total areas under the concentration-time curve (9,200 to 48,000 µg/ml-min). The etoposide mean (± S.D.) terminal half-life of 8.05 ± 4.3 hr and plasma clearance of 28.0 ± 9.7 ml/min/1.73 m², however, were independent of the dosage given. The mean etoposide renal clearance in 5 patients was 10.0 ± 4.3 ml/min/1.73 m², representing from 35 to 40% of the total clearance of this drug from plasma. Cerebrospinal fluid etoposide concentrations ranged from 0.1 to 1.4 µg/ml, as measured in 6 patients at 1 to 8 hr after high-dose etoposide therapy, and were 1.8 ± 1.7% of the simultaneously measured plasma levels. Pleural fluid removed from one patient at 18 hr posttherapy contained etoposide at 1.8 µg/ml. Our data, combined with data published previously, indicate that the pharmacokinetics of high-dose etoposide is linear within the dosage range tested and similar to that seen with lower drug doses. They also suggest that etoposide penetrates poorly into the cerebrospinal fluid.

INTRODUCTION

Etoposide, or VP-16-213, a semisynthetic congener of podophyllotoxin with antineoplastic activity in a number of animal tumor models, was first tested in humans in the 1970s (9, 16). These studies (13, 17, 21) indicated that myelosuppression was the dose-limiting toxicity and that doses of 45 to 250 mg/sq m over the course of 1 to 5 days every 2 to 3 weeks should be used to evaluate the antineoplastic activity of etoposide in specific human tumors. Since that time, etoposide has been demonstrated to be an active agent in the treatment of small-cell lung cancer, various lymphomas, acute nonlymphocyte leukemia, and testicular cancer at doses of 100 to 290 mg/sq m (17, 21).

For many cytotoxic drugs, an escalation of drug dosage usually leads to an increased antitumor effect. For example, in vitro experiments using the K-562 and L1210 (23) tumor lines have shown a progressive increase in cell kill by increasing etoposide concentrations from 1.0 to 100 µg/ml, suggesting that higher doses of this drug may lead to greater therapeutic efficacy in vivo. To exploit this increased efficacy of etoposide and to circumvent its dose-limiting myelosuppression, the technique of autologous bone marrow transplantation of cryopreserved marrow (12) has been used to restore hematopoiesis and allow for increase in drug dosage beyond that normally used. We are using this approach to give etoposide at doses of 400 to 800 mg/sq m/day for 3 consecutive days in conjunction with autologous marrow transplantation to patients with refractory cancers to determine if higher doses do indeed improve the clinical antitumor activity of this drug (22). During these studies, etoposide concentrations in plasma, urine, and CSF3 have been measured to investigate the possible dose dependency in etoposide disposition at these elevated dosages. This report presents the results of these pharmacokinetic studies.

MATERIALS AND METHODS

The effects of high-dose etoposide were examined in 12 patients. Criteria for patient selection included: (a) a biopsy-proven cancer for which no standard therapy was available; (b) age less than 65 years; (c) ambulatory status; (d) normal bone marrow morphology; (e) normal peripheral blood counts (i.e., granulocytes, >1500/µl and platelets, >125,000/µl); (f) no major organ system dysfunction not directly attributable to tumor; and (g) informed consent. All patients had normal renal function (serum creatinine, <1.1 mg/100 ml), except Patient P. S. who had a pretreatment creatinine of 2.6 mg/100 ml. Prior to drug administration, bone marrow was harvested from the patient’s iliac crest and cryopreserved using standard techniques (12). All patients were treated for 3 consecutive days with high-dose (400 to 800 mg/sq m/day) etoposide followed by autologous bone marrow transplantation 72 hr after the last day of etoposide administration. Etoposide (supplied by the National Cancer Institute, Bethesda, Md.), diluted in 0.9% NaCl solution to a maximum concentration of 1 mg/ml, was infused i.v. at 500 mg/hr. All infusion solutions were prepared hourly, and the infusion rate was kept constant by infusing the total dose in equally divided increments over hourly intervals. For example, a dose of 1200 mg was administered as 3 consecutive hourly infusions of 400 mg of etoposide in 500 ml of 0.9% NaCl solution. Thus, each patient received either a 2- or 3-hr daily infusion and an identical daily dose on the next 2 consecutive days. In total, 4 patients were given 400 mg/sq m/day, 4 patients were given 500 mg/sq m/day, 3 patients were given 600 mg/sq m/day, and one patient received 800 mg/sq m/day.

Plasma samples at 0.17, 0.5, 1, 2, 4, 8, 12, and 24 hr after completion of the etoposide infusion were collected and stored at −20° until assayed. Three patients were studied on the first day of their 3 days of treatment, 7 patients were studied on the second infusion day, and 2 patients were studied on the last day of drug administration. Plasma samples collected just prior to drug infusion in patients treated on Days

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P is the plasma etoposide concentration at the midpoint of the urine collection from the literature (1, 6, 7, 10), the effect of drug dose on the collection.

where $U$ is the etoposide urine concentration, $V$ is the urine volume, and $P$ is the plasma etoposide concentration at the midpoint of the urine collection.

RESULTS

The pharmacokinetic parameters of etoposide for each patient are listed in Table 1. By combining these data with those available from the literature (1, 6, 7, 10), the effect of drug dose on the terminal plasma half-life, plasma clearance, peak plasma concentration, and the AUC can be estimated. As noted in Charts 1 and 2, etoposide plasma clearance and terminal plasma half-life were not altered by increases in drug dosage from 100 to 600 mg/sq m. On the other hand, peak plasma etoposide concentrations and AUC measurements increase linearly with the dose of drug administered (Charts 3 and 4) and were best fitted by least-squares linear regression analysis to:

$$
\text{Peak plasma etoposide concentration (µg/ml)} = 0.11 \times \text{etoposide dose administered (mg/sq m)}
$$
where the regression coefficient is 0.98, and

\[ \text{AUC (µg·ml·min)} = 39.4 \times \text{etoposide dose administered} \]

where the regression coefficient is 0.95.

Urinary etoposide clearance measurements made in 5 patients ranged from 5.1 to 14.6 ml/min/sq m with a mean of 10.0 ± 4.3 ml/min/sq m and accounted for 36% of the average plasma clearance of etoposide in this patient population. No consistent change in urinary clearance measurements was noted in 2 patients studied over 3 to 4 consecutive 6-hr collection periods. Twelve- and 24-hr etoposide clearance measurements in these 2 patients were similar to the 6-hr collection measurements. Because etoposide was administered daily over 3 days, the total amount of drug excreted in the urine was not quantitated.

CSF etoposide concentrations were measured in 6 samples from 4 patients following termination of the high-dose etoposide infusion (Table 2). The CSF etoposide concentrations ranged from 0.1 to 1.4 µg/ml and were 1.8 ± 1.7% of simultaneously measured plasma levels. In one patient with a cystic brain tumor, a shunt placed into the tumor cyst and an Ommaya reservoir placed into the lateral ventricle allowed measurements of etoposide concentrations in the tumor fluid, CSF, and plasma at the end of and 4 hr following a 3-hr infusion of etoposide (800 mg/sq m). At the end of the infusion, etoposide concentrations in the tumor, CSF, and plasma were 1.2, 0.5, and 53 µg/ml, respectively, with tumor and plasma levels of 2.5 and 15 µg/ml at 4 hr after administration. Pleural fluid removed from one patient at 18 hr posttherapy contained etoposide at a concentration of 1.8 µg/ml, compared to that patient’s peak plasma etoposide concentration of 25.7 µg/ml and an 18-hr plasma concentration of 0.8 µg/ml.

**DISCUSSION**

Etoposide has been demonstrated to have antineoplastic activity against several human tumors. Its mechanism of antitumor action has not been precisely determined, although it causes metaphase arrest and produces single-strand breaks in DNA (14, 15, 23). Increased cell kill has been noted in K-562 and L-1210 (23) cell lines by increasing etoposide concentrations from 1 to 100 µg/ml. Preliminary clinical studies (11, 22) have also suggested that higher etoposide doses may produce responses in patients refractory to standard drug doses.

All pharmacokinetic studies of etoposide, to date, have been carried out using etoposide doses of 100 to 290 mg/sq m given by i.v. infusion (1, 5, 6, 7, 10). Each of these studies has measured parent drug either by use of radioisotopic techniques (1, 5, 6) or, more recently, by HPLC methods similar to those used in our investigations (7, 10, 19). Our study has attempted to evaluate the pharmacokinetics of etoposide following administration of considerably higher doses (400 to 800 mg/sq m) to determine if the administration of these high doses might alter the pharmacokinetics of this drug. Additional information has been collected regarding etoposide concentrations achievable in the plasma and extravascular compartments following high-dose therapy.

As indicated in Charts 1 and 2, plasma etoposide clearance

### Table 2

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sample method</th>
<th>Etoposide dose (mg/sq m)</th>
<th>Time of sampling (hr)</th>
<th>CSF concentration (µg/ml)</th>
<th>Plasma concentration (µg/ml)</th>
<th>CSF/plasma (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N.T.</td>
<td>Ommaya</td>
<td>400</td>
<td>2</td>
<td>0.1</td>
<td>18</td>
<td>0.6</td>
</tr>
<tr>
<td>J.B.</td>
<td>L.P.</td>
<td>600</td>
<td>4</td>
<td>0.3</td>
<td>24</td>
<td>1.1</td>
</tr>
<tr>
<td>B.R.</td>
<td>Ommaya</td>
<td>600</td>
<td>1</td>
<td>1.4</td>
<td>30</td>
<td>4.7</td>
</tr>
<tr>
<td>D.H.</td>
<td>Ommaya</td>
<td>800</td>
<td>0</td>
<td>0.5</td>
<td>53</td>
<td>0.9</td>
</tr>
</tbody>
</table>
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Rates and the terminal etoposide plasma half-life are not altered by increasing the dose of drug. In contrast, peak plasma etoposide concentrations and etoposide areas under the concentration-time curve are directly and linearly related to the dose of drug administered. These relationships, compiled from previous studies and from our own data, show large S.D.s at any given dose of drug, indicating significant interpatient variability in the handling of etoposide. The good linear correlation (r = 0.95) between the mean area under the plasma etoposide concentration-time curve and drug dosage, however, indicates that, at high doses of etoposide (up to 600 mg/sq m), the plasma clearance mechanisms of this drug remain unaltered. Urinary clearance of intact drug accounts for approximately 36% of plasma clearance. Because of the significant percentage of intact drug cleared by the kidney, dose reductions may need to be made in the presence of severe renal insufficiency to prevent excess toxicity. The elimination fate of the remaining 60% of drug is uncertain. Early studies using radiolabeled drug indicated that 0 to 16% of an administered drug dose can be recovered in the stool (6), and a recent study using HPLC techniques has been unable to detect significant intact drug in the bile of a patient receiving etoposide (8). Etoposide metabolism has not been well determined. The hydroxy-acid and picrolactone isomers of etoposide have been identified by some investigators (5, 10) but not by others (19). In preliminary studies, we have found low concentrations of both of these etoposide metabolites in plasma and urine of patients receiving high-dose therapy.

Measurements of CSF in several patients and the etoposide concentration found in fluid from a cystic brain tumor in one patient indicate poor penetration of etoposide across the blood-brain barrier. Etoposide has been shown to have particular activity against lymphomas and small-cell lung cancer. Both of these diseases have a high frequency of metastasis to the brain and/or meninges. Because CSF concentrations are only 1 to 2% of concomitant plasma levels, etoposide would not appear to be a useful drug in preventing or treating metastasis. However, with high-dose etoposide therapy (800 mg/sq m/day for 3 days), a 0.2- to 1.0-g/ml CSF etoposide concentration can be maintained for at least 3 days. Evaluation of etoposide cytotoxicity in cell cultures suggests that this may be a cytotoxic drug concentration at that duration of exposure for some cell lines. Etoposide also poorly penetrated into the pleural fluid of the single patient in whom measurements were made.

In summary, this study provides some additional useful information on the dose dependency of etoposide and its penetration into extravascular sites which may be of use to physicians when attempting to increase etoposide dose. With the recent use of the "tumor stem cell" assay system for determining drug resistance or sensitivity (18), such pharmacokinetic data may become increasingly important in individualizing drug doses to obtain maximal clinical effectiveness. Our data indicate that the pharmacokinetics of high-dose etoposide are similar to those seen with low drug doses, that renal etoposide clearance accounts for 35 to 40% of total plasma clearance, and that etoposide penetrates poorly into the CSF and probably into brain tumors and pleural fluid.

REFERENCES

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