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A case report and description of the pharmacokinetic behavior of intrapleurally instilled etoposide

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Summary. *Etoposide, at a dosage of 100 mg/m² (156 mg in 250 ml 0.154 M NaCl), was instilled through a thoracostomy tube into the left pleural cavity of a 60-year-old woman with diffuse histiocytic lymphoma and a refractory, recurrent, malignant left pleural effusion. Etoposide concentrations in plasma and pleural cavity fluid were measured by a reverse-phase HPLC system with a C_{18}-reverse phase column, a mobile phase of methanol: H_2O (55 : 45) pumped at 1.2 ml/min, and detection by absorbance at 254 nm. Pleurodesis was successfully accomplished by this maneuver and there were no adverse clinical consequences. Absorption of etoposide from the pleural cavity was slow (approximately 0.2 ml/min). The pleural cavity exposure to etoposide, as measured by the area under the curve, was 46 times greater than if a similar dose had been given IV. Conversely, systemic exposure to etoposide, as assessed by plasma AUC, was less than 50% that associated with IV injection of a similar dose.*

Introduction

Tumor-related effusion in closed body spaces such as pleural and peritoneal cavities can present difficult management problems [8]. Intermittent and chronic drainage, as well as instillation of sclerosing or antineoplastic agents, have been advocated to alleviate the symptoms associated with such effusions [1, 5, 7, 9]. Instillation of specifically active agents has long been advocated for a variety of tumors [1, 7, 9]; however, the pharmacokinetic behavior of many antineoplastic drugs is not well documented after closed space administration. We recently had the opportunity to study the clinical and pharmacokinetic consequences of intrapleural instillation of etoposide.

Case history

In April, 1982, a 60-year-old white woman first noted a right neck mass, biopsy of which revealed diffuse histiocytic lymphoma. She underwent a staging evaluation in which bilateral bone marrow aspirates and biopsies, lumbar puncture, and computer-assisted tomograms were all negative for tumor. A staging laparotomy without splenectomy was performed, and no extranodal disease was detected within the abdomen. After surgery, the patient was staged IIIA and was treated with combination chemotherapy, receiving three courses of cyclophosphamide, doxorubicin, vincristine, and prednisone (CAVP) plus intrathecal methotrexate. A partial response was achieved. Further chemotherapy consisted of cisplatin, bleomycin, and vinblastine for three courses, followed by three more courses of CAVP. Noninvasive restaging, at 12 months after diagnosis, showed the patient to be in complete remission.

Four months later, the patient developed a small-bowel obstruction. Exploratory laparotomy revealed a large mass in the terminal ileum and cecum, large mesenteric lymph nodes, and ascites. An open liver biopsy was negative, but the ascitic fluid contained malignant cells and the mass proved to be recurrent disease. Resection of the terminal ileum and a right hemicolectomy with reanastomosis were performed. One week postoperatively, the patient developed bilateral pleural effusions and ascites. Both the pleural fluid and the ascitic fluid contained malignant cells. Repeated thoracenteses (both right- and left-sided) were performed because of rapid reaccumulation of the pleural effusions. Chemotherapy was initiated with etoposide, methotrexate (with citrovorum factor), and cytosine arabinoside [6]. Despite systemic chemotherapy, bilateral pleural effusions recurred. Because of the symptomatic nature of the effusions, a right-sided thoracostomy tube was inserted and tetracycline pleurodesis was performed. All cultures of the pleural fluid were repeatedly negative for acid-fast bacilli, fungi, and bacterial pathogens. The patient was discharged from the hospital and received two additional courses of combination chemotherapy as an outpatient.

Three months later, the patient presented complaining of night sweats, low-grade fever, weight loss, and increased dyspnea. Physical examination revealed a temperature of 37.6° C, blood pressure 100/60, and respiratory rate of 22. Bibasilar rales were present on chest examination. The heart rate was 120 with an S4 gallop. No pericardial rub was present. Abdominal examination revealed no ascites or hepatosplenomegaly. A small left axillary lymph node was present. Chest roentgenogram demonstrated a recurrent, left pleural effusion with no evidence of pleural fibrotic changes. Thoracentesis recovered fluid containing numerous malignant lymphoid cells, and cultures of the fluid were again negative for all pathogens. Computer-assisted tomograms of the chest revealed no hilar or mediastinal adenopathy and no pulmonary parenchymal disease. Large bilateral pleural effusions and pericardial thickening were present. Computer-assisted tomograms of the abdomen and pelvis showed mesenteric involvement, which was improved in comparison to previous scans, as well as resolution of the previously noted ascites. The patient

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was, therefore, felt to have a mixed response to chemothearpy, and local measures to control the symptomatic effusions were deemed appropriate.

A thoracostomy tube was inserted into the left pleural space and the effusion was drained completely. In an attempt to effect local control of the pleural disease, etoposide 100 mg/m^2 was administered into the left pleural cavity. A total dose of 156 mg etoposide in 250 ml 0.154 *M* NaCl was instilled, and the chest tube was clamped for the next 4 h. While the tube was clamped, the patient's position was changed every 20 min (supine, left lateral, right lateral, and prone) to expose the entire pleural surface to the drug. When the tube was unclamped, it drained 75 ml fluid immediately and an additional 220 ml over the next 18 h. The chest tube drainage averaged 60 ml/day over the next 3 days. The chest tube was then removed. Two days after intrapleural etoposide instillation, the patient received etoposide (100 mg/m^2) IV, and also methotrexate, cytosine arabinoside, and citrovorum.

Materials and methods

Samples of heparinized blood and pleural fluid were collected at specified times after intrapleural instillation of etoposide. Blood and pleural fluid were centrifuged at 1,000 *g* for 10 min and supernatants were removed and stored at −20° C until the time of assay.

Etoposide was analyzed by the HPLC method of Strife and Jardine [10]. Briefly, 1 ml plasma or pleural fluid was extracted with 5 ml chloroform containing 10 μg/ml VM 26 as an internal standard. Of the resulting chloroform layer, 4 ml was evaporated to dryness under nitrogen. Samples were reconstituted in 50 μl methanol and 40 μl was injected onto the HPLC. The HPLC system consisted of a Spectra-Physics (Santa Clara, Calif) model 3500B HPLC fitted with an Alltech C_{18} column (10 μm, 25 cm × 4.6 mm) (Alltech, Deerfied, Ill) and a C_{18} guard column (30–38 μm, 5 cm). The mobile phase was methanol : water (55 : 45), pumped at a flow rate of 1.2 ml/min. Absorbance at 254 nm was monitored with a Spectra-Flow model 770 detector (Schoeffel Instrument Co., Westwood, NJ), and displayed on a Hewlett-Packard 7130A stripchart recorder (Palo Alto, Calif). Peak areas were integrated with an Autolab System I computer (Spectra-Physics), and etoposide concentrations were determined by comparison with the area of the internal standard peak. The areas under the curves (AUC) of plasma or pleural fluid etoposide concentration vs time were evaluated by the trapezoidal rule.

Results

Clinical

The patient tolerated the intrapleural instillation of etoposide well, although she required two additional doses of IM morphine sulfate for pain control. She had been receiving this narcotic analgesic for control of pain related to the thoracostomy tube prior to etoposide administration intrapleurally. She felt that the pain was equal to or slightly more intense than that she had experienced with tetracycline pleurodesis. After the thoracostomy tube was removed, no reaccumulation of pleural fluid occurred. Subsequent chest roentgenograms showed chronic pleural scarring with no significant pleural effusion.

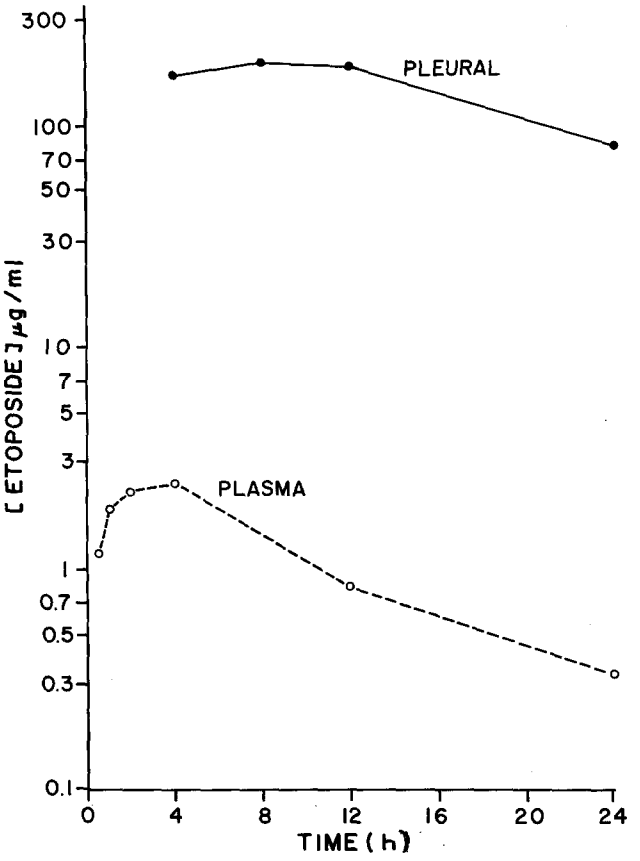

Fig. 1. Plasma (○———○) and pleural fluid (●———●) concentrations of etoposide measured at various times after instillation of 100 mg/m^2 (156 mg in 250 ml 0.154 *M* NaCl) etoposide into the left pleural cavity. Etoposide concentrations were determined by HPLC as described in *Materials and methods*

Pharmacokinetics

A solution of 624 μg/ml etoposide had been injected into the drained pleural cavity and our measurements showed a concentration of 170 μg/ml 4 h later (Fig. 1). The concentration of etoposide in the pleural fluid remained relatively constant for 12 h. The concentration of drug was still 79 μg/ml at 24 h after instillation into the pleural cavity. Plasma concentrations of etoposide were much lower than those observed in the pleural fluid (Fig. 1). The highest plasma concentration observed was 2.5 μg/ml and occurred 4 h after drug instillation. This was less than 2% of the concomitant pleural fluid concentration. Unlike pleural fluid concentrations, plasma concentrations of etoposide dropped to less than 0.8 μg/ml at 24 h after injection. The AUC for pleural fluid etoposide was 346,800 μg/ml × min while the plasma AUC was only 1,650 μg/ml × min.

Discussion

Intracavitary drug administration has long been advocated [1, 7, 9]; however, the number of agents tested is limited and the pharmacokinetics of this approach are even less well documented. The theoretical advantages for intrapleural and intraperitoneal administration have recently been reviewed [2], and include increased local concentration and prolongation of drug exposure. In vitro evidence has suggested that both are

important to etoposide activity [3], making this a potentially attractive agent for intracavitary administration.

This patient provided an opportunity to begin to explore some of the open clinical and pharmacokinetic questions with regard to the potential advantages of regional etoposide administration. Intrapleural administration of etoposide did prove successful in this case. Pleurodesis was accomplished, with no return of the patient's pleural effusion after 12 weeks.

Consideration of pleural and plasma etoposide AUCs shows that the targeted area experienced 210 times greater exposure to the drug than did the plasma. Using formulae and relationships suggested by Collins [2], one can calculate that the pleural drug exposure was 46 times more than it would have been after IV administration of the same etoposide dose [4]. At the same time, the body, perfused by the systemic circulation, was exposed to less than half the amount of drug to which it would have been exposed after IV administration of the same dose [4].

With the data from this patient, it is possible to make a first approximation of the rate of absorption of etoposide from the pleural space into the plasma. Based on the rates of plasma clearance in 13 patients treated IV with etoposide at a dose of 100 mg/m^2 [4], the average rate of plasma clearance for etoposide is 27.6 ± 2.6 ml/min/m^2. Considering this patient's body surface area, her rate of plasma clearance would have been approximately 41 ml/min. In theory, the overall selectivity achieved by regional administration of the drug, R_d, is expressed by the equation: $R_d = 1 + CL_{TB}/Q$, where CL_{TB} is the rate of clearance of the drug and Q is the rate of infusion into the plasma. In the patient under discussion, the overall selectivity, as mentioned earlier, was 210. Accordingly, it is possible to calculate the rate of absorption of etoposide from the pleural cavity into plasma as 0.20 ml/min. This value seems reasonable when compared with the absorption rates of 0.5–5 ml/min reported for intrathecally administered drugs and approximately 10 ml/min reported for IP administered drugs [2].

The pharmacokinetic data presented here document both a high local concentration and a slow systemic absorption of etoposide, resulting in prolonged exposure of malignant cells involving the pleural surface to high concentrations of drug. Furthermore, the plasma concentrations and plasma AUC observed after intrapleural etoposide instillation were relatively low, suggesting the possibility of either increasing the dose instilled into the pleural space or giving concurrent IV etoposide. The relative lack of toxicity in this case, together with the above considerations, suggests that etoposide may be a useful drug for intrapleural instillation.

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