By using UV detection at 225 nm the lower limit of detection is less than 100 mg/ml in a 0.5 ml plasma sample. In patients receiving VP16-213 (200 mg/m^2) as an intravenous infusion over 30 min. The drug follows either 2 or 3 compartment kinetics, with half-lives of the second phase of 6–8 h, and of the third phase (where detected) of 20–46 h.

Bioavailability has been assessed in five patients who have received 400 mg VP16-213 both as an i.v. infusion and orally in capsules, and estimates of bioavailability using both area under the curve and urinary recovery methods range from 48%–78%.

Renal clearance of VP16-213 is about 10–15 ml/min, and accounts for one third of the total plasma clearance.

**Sensitive High Performance Liquid Chromatographic Analysis of VM26, VP16-213 and Cis-Hydroxy Acid of VP16-213 Using UV and Electrochemical Detection**

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This paper presents a rapid and sensitive high performance liquid chromatographic assay of the two antineoplastic podophyllotoxine analogs VP16-213 and VM26 in plasma and urine. The drugs are extracted after adding of an internal standard (Ethyl ester of p-hydroxy benzoic acid) with 1 ml chloroform. After washing and evaporation of the organic layer the extracts are chromatographed on a LiChrosorb reversed phase C18 column using uv detection at 280 nm. Quantitation is based on peak height ratios. The quantitation limits are 30 ng VP16-213/ml plasma and 50 ng VM26/ml plasma. This paper also presents an hplc method for the analysis of the cis-hydroxy acid of VP16-213, an isomer of a possible metabolite of VP16-213. Since no synthesis of this metabolite, trans-hydroxy acid of VP16-213, has been reported the investigations are carried out on the cis-isomer. Lower quantitation and detection limits of VM26, VP16-213 and possible metabolites, due to higher sensitivity and selectivity, will be achieved by using an hplc method with electrochemical detection. The applied electrochemical detector consists of a flow-through cell with two glassy carbon (Work and auxiliary) electrodes and an Ag-AgCl reference electrode. The electrochemical potential is set at +1100 mV vs. Ag/AgCl reference electrode. The detection limit of VP16-213 in this system is 100 pg absolute amount injected. Further preliminary clinical pharmacokinetic results will be presented.

**Analysis of VP16-213 and VM26 in Plasma by High Performance Liquid Chromatography with UV and or Fluorescence Detection**

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A rapid, convenient, sensitive and specific high-performance liquid chromatographic (HPLC) procedure for the analysis of plasma levels of VP16-213 and VM26 has been developed.

The drugs are extracted from plasma with chloroform. The extracts are then evaporated to dryness, reconstituted in methanol, and chromatographed on a reverse-phase microparticle C18 column using isocratic elution with a mixture of methanol and water (60:40). Each drug is used as the internal standard for the other. Quantitation to 500 ng/ml (850 pmole/ml) of plasma is obtained using UV detection at 254 nm and measuring peak height ratios.

The drugs can be quantitated conveniently to at least 50 ng/ml (85 pmole/ml) of plasma when fluorescence detection of these compounds is employed (excitation at 215 nm; emission at 328 nm). The increased sensitivity of the fluorescence assay allows quantitation of these drugs in plasma to at least 48 h with normal dosages. The increased specificity of fluorescence detection also allows quantitation of VP16-213 and VM26 in the presence of coadministered drugs which can interfere with the UV assay.

**A Phase I—II Trial of Continuous Infusion VP16-213**


Since there appears to be a time-dose response relationship for VP16-213, the current dose seeking study of 5 day continuous infusion was initiated on a q3 week schedule. Patients not candidates for other treatments were started at 75 mg/m^2/day × 5 day and subsequent trials were escalated if there were acceptable toxicity. All patients had received prior chemotherapy and 59% had received prior irradiation. The tumors included: metastatic basal cell CA (1), Breast CA (1), colon CA (2), squamous lung cancer (1), oat cell (2), peritoneal sarcoma (1) mixed mesodermal tumor (1). The median age was 55 (range 31–65) and the median performance status was 70 (range 50–90).