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SHORT COMMUNICATION

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Biliary excretion of etoposide in children with cancer

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Abstract *Purpose*: Two children with soft tissue sarcomas receiving etoposide as part of their standard clinical treatment had external biliary drainage due to obstruction of the bile duct. These unusual cases provided an opportunity to investigate the biliary clearance of etoposide by determining etoposide concentrations in bile and plasma samples obtained during chemotherapy. *Patients and methods*: Etoposide was administered to patient 1 at a dose of 150 mg/m^2, as a 4 h infusion, on each of three days of treatment. Patient 2 received a daily etoposide dose of 800 mg/m^2 as a 24 h continuous infusion, also over a 3-day treatment period. Bile and plasma samples were obtained at regular intervals from both patients and etoposide levels quantified by LC/MS analysis. *Results and discussion*: Biliary etoposide clearance was approximately equal to the flow of bile, with an average clearance of 0.32 ml/min determined in patient 1. Less than 2% of the etoposide dose administered was excreted in the bile in either patient studied, indicating that biliary clearance of etoposide is relatively minor. These results suggest that etoposide dose adjustment is unnecessary in patients with biliary obstruction.

Keywords Etoposide · Bile · Paediatric · Pharmacokinetics

Introduction

Etoposide is a widely used anticancer agent in the treatment of both adult and childhood malignancies. Several studies have been published concerning the disposition of this agent in disease states, defining the pharmacokinetic parameters of etoposide and indicating that the drug is cleared by both renal and non-renal processes [1, 7, 8]. However, there is limited information concerning the clearance of etoposide in the bile. We have studied two children with soft tissue sarcomas, both of whom had free external biliary drainage, thus allowing the parallel collection of bile and plasma samples following etoposide administration. Treatment of these two patients provided a rare opportunity to quantify etoposide concentrations in both bile and plasma and therefore investigate the importance of biliary clearance of etoposide in children with cancer.

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Patients and methods

Patients

Case 1

The first patient was a 3-year-old boy, presenting with a 3 week history of jaundice, who was diagnosed with a hepatic embryonal rhabdomyosarcoma following an open biopsy. Pulmonary metastases were present at diagnosis. Liver function was abnormal, with a serum bilirubin level of 115 μmol/l, alkaline phosphatase 1,013 U/l and alanine transaminase 304 U/l. Initial chemotherapy with carboplatin and etoposide was selected due to severe biliary obstruction which may have led to unpredictable toxicities from alternative agents such as ifosfamide, vincristine, actinomycin and epirubicin. No response was observed to this combination and bile duct obstruction became more severe (serum bilirubin increased to 271 μmol/l). Percutaneous cholangiography was performed and the catheter tube left in situ, allowing free external drainage of bile. Liver function rapidly improved and it was subsequently possible to administer ifosfamide, vincristine and etoposide. Three courses of this chemotherapy were successfully

administered with the drain in situ and minimal toxicity was observed. A good tumour response was obtained and complete surgical resection was achieved. The patient continued with chemotherapy according to current national treatment guidelines (SIOP MMT98 protocol) with later resection of pulmonary metastases and is now alive with no evaluable disease 3.5 years from diagnosis and 2.5 years from the end of treatment.

Case 2

The second patient was a 15-year-old girl who presented with a history of haematemesis and melaena after a week of persistent vomiting. She had a complex medical history and had been treated for an adrenocortical carcinoma at age 2, for which she underwent surgery and radiotherapy. Initial investigations showed liver dysfunction, with a serum bilirubin level of 100 μmol/l, alkaline phosphatase 568 U/l, alanine transaminase 288 U/l. Ultrasound, CT and MR imaging showed a mass in the porta hepatis, causing complete obstruction of the common bile duct. The mass was biopsied and pathology was consistent with a high grade leiomyosarcoma. The patient underwent laparoscopic gastroenterostomy to bypass the obstruction, with external biliary drainage achieved at the same time. She subsequently began treatment with high dose cyclophosphamide followed 3 weeks later by high dose etoposide, both of which were poorly tolerated. Despite some initial clinical improvement, increasing tumour burden made her illness progress and she died 4 months after presentation.

Treatment

Etoposide was administered to patient 1 at a dose of 150 mg/m^2, as a 4 h infusion, on each of 3 days of treatment. Patient 2 received a daily etoposide dose of 800 mg/m^2 as a 24 h continuous infusion, also over a 3 day treatment period. Bile samples were obtained for pharmacokinetic analysis at regular intervals over the 3 days of etoposide chemotherapy for patient 1 and over a 48 h period for patient 2. Total volumes of bile collected were approximately 420 ml for patient 1 and 210 ml patient 2. Blood samples were obtained during the first 2 days of chemotherapy for patient 1 and over the entire treatment period for patient 2.

Pharmacokinetic analysis

Plasma was separated from whole blood samples by centrifugation (1200 *g*, 4°C, 10 min) and all samples were stored at −20°C prior to analysis by liquid chromatography-mass spectrometry (LC/MS). Analysis was performed using an API 2000 LC/MS/MS with analyst software (Applied Biosystems, CA, USA) following separation of etoposide on a Genesis C_{18} column with a mobile phase of acetonitrile:0.1% acetic acid pH 4.7 (50:50) at a flow rate of 0.2 ml/min. Bile and plasma samples (100 μl) were extracted with ethyl acetate and etoposide concentrations quantified using a standard curve of 0.10–10.0 μg/ml. For the determination of etoposide concentrations in bile, standards and quality assurance (QA) samples were prepared using pre-treatment bile obtained from these patients. The calibration plots were linear over the concentration range studied (r^2 0.998) and the assay had a limit of quantitation of 0.1 μg/ml. The biliary elimination rate was calculated from the amount of etoposide recovered (etoposide concentration × volume of bile) divided by the collection interval. Biliary clearance was then calculated from the ratio of biliary elimination rate to plasma concentration for each collection period.

Results and discussion

Plasma and bile etoposide concentrations determined during the 3 days of etoposide treatment for patient 1 are shown in Fig. 1. Biliary etoposide concentrations mirrored those in plasma, with comparable C_{max} and T_{max} values. Etoposide plasma pharmacokinetic parameters on day 1 of treatment were determined using non-compartmental analysis in WinNonLin. A clearance of 49.4 ml/min was calculated, with an elimination half-life ($T_{1/2\beta}$) of 5.3 h. These data are comparable with those previously reported by other groups in a paediatric patient population without biliary impairment [2, 3]. Biliary etoposide clearance was approximately equal to the flow of bile, with an average clearance of 0.32 ml/min. This is less than 1% of the total clearance, in agreement with a previously published report [4], suggesting that renal elimination, metabolism and/or biliary excretion of metabolites makes a greater contribution to total clearance. A mean steady-state etoposide plasma concentration of 26.0 μg/ml was observed in patient 2, following a continuous infusion of 800 mg/m^2/day, as compared to a mean bile etoposide concentration of 113.2 μg/ml. In this patient, 1.5% of the dose was excreted in the bile, suggesting that biliary excretion may be higher when the dose of etoposide is increased. No additional peaks were observed in bile samples collected following etoposide administration, suggesting that significant metabolism did not occur.

Elimination of etoposide by the liver may involve excretion of unchanged drug into bile, or metabolism and subsequent excretion by the hepatic or renal route. Etoposide is also known to be highly protein bound [6] and hence hepatic dysfunction may also indirectly alter the disposition of the drug as a result of hypoproteinaemia. The total plasma clearance of etoposide has previously been shown to be increased in patients with liver dysfunction in a study of patients with widely varying hepatic and renal functions [9]. This study indicated that

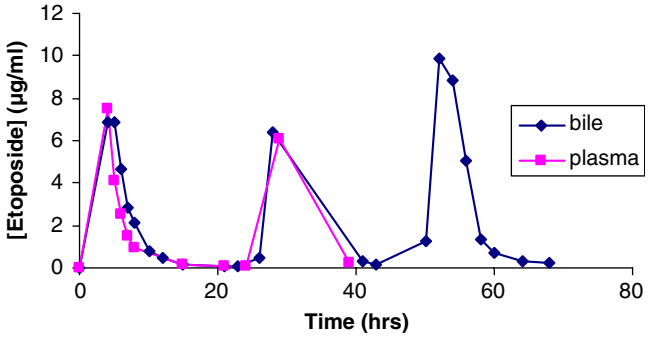

Fig. 1 Etoposide concentrations in plasma and bile following administration of etoposide (150 mg/m^2) as a 4 h infusion on each of 3 days of treatment

patients with serum bilirubin greater than 17 µM had a higher total clearance compared to those with no elevation of serum bilirubin. However, the fraction of unbound etoposide was significantly increased and the plasma clearance of unbound etoposide was lower in patients with raised serum bilirubin. An increase in systemic exposure to unbound etoposide was therefore seen, despite an overall reduction in the total drug exposure. The possibility of an increase in drug toxicity being associated with liver dysfunction may therefore necessitate etoposide dosage adjustment in this patient group. Dose reductions have previously been indicated in patients with impaired liver function in a study which showed correlations between low serum albumin levels, high free etoposide exposures and increased haematological toxicity [5].

The data published in the current study indicate parallel pharmacokinetic profiles observed in bile and plasma following a 4 h intravenous infusion of etoposide in a child with embryonal rhabdomyosarcoma. The average biliary clearance in this patient was 0.32 ml/min, less than 1% of total plasma clearance. Comparable results were obtained from a second child studied on a continuous infusion dosage regimen, with biliary clearance accounting for approximately 1.5% of the total etoposide clearance. These data suggest that biliary clearance of etoposide is relatively minor and that dose adjustment is unnecessary in patients with biliary obstruction.

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