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SHORT COMMUNICATION

Olaf van Tellingen · Maarten T. Kuck
L. Thomas Vlasveld · Sjoerd Rodenhuis
Willem J. Nooijen · Jos H. Beijnen

Unchanged pharmacokinetics of etoposide given by intra-arterial hepatic infusion as compared with i.v. infusion

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Abstract We investigated the pharmacokinetics of etoposide given to a patient suffering from multifocal liver metastases from an unknown primary tumor. The drug was given either by i.v. infusion or by hepatic arterial infusion (HAI). The calculated pharmacokinetic parameters (mean values ± SD) were similar after i.v. infusion and HAI, viz., 6.4 ± 0.7 versus 6.5 ± 0.2 h for the terminal elimination half-life ($t_{1/2}\beta$), 98.5 ± 1.3 versus 101.3 ± 5.9 mg l^{-1} h for the area under the plasma concentration-time curve (AUC), 21.2 ± 0.3 versus 20.6 ± 1.2 ml $min^{-1} m^{-2}$ for clearance (Cl), 17.7 ± 1.9 versus 18.1 ± 2.6 mg/l for the peak concentration, and 11.7 ± 1.3 versus 11.6 ± 1.0 l/m^2 for the volume of distribution (V_d), respectively. We therefore conclude that administration of etoposide by HAI does not result in a significantly higher liver extraction. Hepatic extraction of etoposide is determined by the fraction of non-protein-bound (free) drug present. The lack of a difference between the two administration routes suggests that under in vivo conditions the equilibrium between free and bound drug is established before the drug reaches the hepatic arterioles. Consequently, administration by HAI does not lead to an increased exposure of the tumor in the liver to free (active) etoposide. Furthermore, the overall exposure of the liver to total (bound + free) etoposide is increased only from about 100 to 120 mg l^{-1} h. These results do not favor the use of this more complex route of drug administration in the treatment of (metastatic) cancer located in the liver.

Key words Etoposide · Intra-arterial infusion · Liver · Pharmacokinetics

O. van Tellingen (✉) · W.J. Nooijen
Department of Clinical Chemistry, The Netherlands Cancer Institute/Antoni van Leeuwenhoekhuis, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

L.T. Vlasveld[1] · S. Rodenhuis
Department of Medical Oncology, The Netherlands Cancer Institute/Antoni van Leeuwenhoekhuis, Amsterdam, The Netherlands

M.T. Kuck · J.H. Beijnen
Department of Pharmacy, Slotervaartziekenhuis, Amsterdam, The Netherlands

Present address:
[1]Diaconessen Ziekenhuis, Eindhoven, The Netherlands

Introduction

Etoposide (Vepesid; VP16-213) is a glycoside derivative of podophyllotoxin, which plays a major role in the management of a variety of neoplastic disorders when given either as a single agent or in combination with other cytotoxic drugs. The pharmacokinetic behavior of etoposide after i.v. or oral administration has been thoroughly investigated (for an overview see Slevin [9]) and is characterized by considerable interpatient variability. The profile of the plasma concentration-time curve after i.v. infusion follows two-compartmental decay kinetics, with the terminal half-life ranging between 4 and 9 h. The major part (94%) of the drug is bound to plasma proteins (mainly albumin) [1]. The relatively low distribution volume (about 10 l/m^2) suggests the absence of a transport system that would mediate a facilitated influx of etoposide into cells. The tissue distribution thus rests on passive diffusion of free (non-protein-bound) drug. Locoregional drug delivery into the peritoneal or pleural cavity has also been described. These studies confirmed the theoretical consideration that intracavitary administration would lead to an increase in local drug exposure, since both the area under the concentration-time curve (AUC) of the total drug and the fraction of free drug were increased [3, 4, 14].

Recently a Japanese study provided some evidence for an improved antitumor efficacy of hepatic arterial infusion (HAI) versus i.v. administration in hepatocellular carcinoma [13]. In this paper we present the results of a pharmacokinetics study in which etoposide was given to a patient suffering from multifocal liver metastases from an unknown primary tumor. In this study the patient received the drug in separate courses either by i.v. infusion or by HAI. The design of this study offered a unique opportunity to explore the possible impact on the pharmacokinetics of etoposide caused by administration just before the main metabolic organ.

Case report

A 43-year-old Caucasian man was referred to our institute because of multiple hepatic metastases from an unknown primary tumor. Examination of a cytological punctate was compatible with adenocarcinoma. Because of a strongly elevated serum alpha fetoprotein (AFP) level of 73,000 ng/ml (normal < 10 ng/ml) with 50% concavalin binding and the atypical angiographic pattern, an extragonadal germ-cell tumor had to be differentiated from a multifocal hepatocellular carcinoma. Six courses of chemotherapy consisting of cisplatin (20 mg/m^2 given on days 1–5), etoposide (120 mg/m^2 given on days 1, 3, and 5), and bleomycin (30 mg given on days 2, 9, and 16; courses 1–4 only) resulted in a normalization of the serum AFP level and of liver-function tests (the serum bilirubin value decreased from 46 to 5 μmol/l) without significant tumor regression as determined from a computed tomography (CT) scan of the liver. Within 1 month the serum AFP level started to rise again. Although the tumor was not very vascular as determined by angiography, we decided to infuse cisplatin (CDDP) and etoposide into the hepatic artery through an implanted arterial access device. The chemotherapy scheme was as follows:

1. Course 1 – VP16-213 given at 125 mg/m^2 per day on days 1–3 over 1 h by HAI and CDDP given at 50 mg/m^2 per day on day 1 over 24 h by HAI
2. Course 2 – CDDP given at 50 mg/m^2 per day on day 1 over 24 h HAI
3. Course 3 – VP16-213 given at 125 mg/m^2 per day on days 1–3 over 1 h by i.v. infusion and CDDP given at 50 mg/m^2 per day on day 1 over 24 h by HAI
4. Courses 4, 6, and 8 – same as course 2
5. Courses 5, 7, and 9 – same as course 3

The liver-enzyme values were only moderately elevated prior to the first course of chemotherapy and returned to their normal values during the chemotherapy (Table 1). Bilirubin, albumin, and total protein levels remained normal throughout the whole period. After five courses the serum AFP level had decreased from 4400 to 50 ng/ml, with significant tumor regression being apparent on the CT scan of the liver. Because of the persistent absence of extrahepatic tumor involvement, the patient underwent an uneventful orthoptic liver transplantation at King's College in London. The histology pattern was reported to be consistent with that of a cholangiocarcinoma.

For purposes of drug determination, on days 1–3 of courses 1 and 3, heparinized venous blood samples were drawn from an arm at $t = 15$ and 30 min at $t = 1$ (top), 2, 3, 5, 9, and 24 h (just prior to the next infusion). Samples were centrifuged and the plasma was frozen (-20°C) immediately for later analysis. Analysis of the total (bound and unbound) drug plasma levels was performed by high-performance liquid chromatography (HPLC) using a method based on the work of Sinkule and Evans [8]. Pharmacokinetic modeling of plasma concentration-time curves was performed with the MW\Pharm software package (version 3.02; Medi\Ware, Groningen, The Netherlands) [5].

Table 1 Blood-chemistry parameters determined during the chemotherapy

Compound(normal values)	1 day before course 1	1 day before course 3	1 week after course 9
Alkaline phosphatase (35–110U/1)	259	174	110
5'-Nucleotidase(< 11 U/1)	31.3	15.3	6.3
Aspartate aminotransferase(< 17 U/1)	34	14	9
Alanine aminotransferase (< 21 U/1)	47	24	13
γ-Glutamyl transferase (6–28 U/1)	95	46	30
Bilirubin (< 17 μmol/l)	7	6	5
Albumin (35–55 g/l)	45	49	52
Total protein	74	79	79

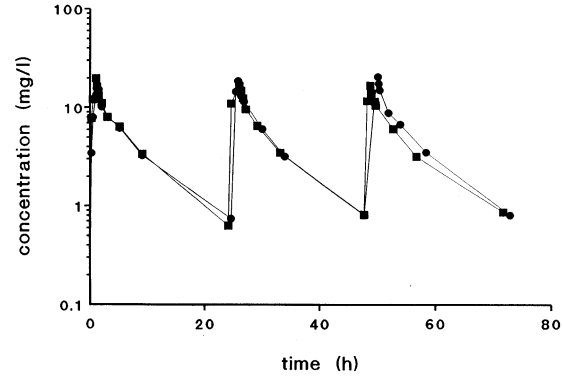

Fig. 1 Concentration versus time curves generated for etoposide infused into the hepatic artery (*circles*) or i.v. (*squares*)

Results and discussion

The plasma concentration versus time curves generated for etoposide after HAI and i.v. administration were superimposable (Fig. 1). Consequently, the calculated pharmacokinetic parameters were similar (Table 2) and in line with those reported previously [9]. Only slight variability was observed between the subsequent courses.

The pharmacokinetic behavior of etoposide is dominated by the high plasma-protein binding of the drug [1]. Despite its hydrophobic structure, which should facilitate passive diffusion through cellular membranes, the volume of distribution is low, indicating poor tissue penetration. As protein binding is correlated with serum albumin and bilirubin concentrations and because at the time of this study the values for these

Table 2 Summary of the pharmacokinetic parameters of etoposide determined after i.v. infusion and HAI[a]

Route	Day	$t_{1/2}(\alpha)$ (h)	$t_{1/2}(\beta)$ (h)	C_{max} (mg/l)	$AUC_{0-24\,h}$ ($mg\,l^{-1}\,h$)	Cl($ml\,min^{-1}m^{-2}$)	V_d ($1/m^2$)
Intravenous	1	0.38	5.7	19.9	99.3	21.0	10.4
	2	0.23	6.3	16.7	97.0	21.5	11.7
	3	0.64	7.2	16.6	99.2	21.0	12.9
	Mean	0.42	6.4	17.7	98.5	21.2	11.7
	SD	0.21	0.7	1.9	1.3	0.3	1.3
HAI	1	0.51	6.7	15.3	96.5	21.5	12.5
	2	0.49	6.5	18.6	99.4	21.0	11.8
	3	0.40	6.3	20.4	107.9	19.3	10.5
	Mean	0.47	6.5	18.1	101.3	20.6	11.6
	SD	0.06	0.2	2.6	5.9	1.2	1.0

[a] $t_{1/2}(\alpha)$, $t_{1/2}(\beta)$ Half-lives during the α and β phase, respectively, C_{max} systemic peak plasma level; AUC area under the concentration-time curve (not extrapolated to infinity); Cl clearance; V_d volume of distribution

parameters were within their normal limits in this patient, a free (unbound) fraction (f_u) of etoposide amounting to $4.3 \pm 0.4\%$ may be assumed [10]. Although many details on the fate of etoposide remain unresolved, it is evident that metabolism is an important elimination pathway, since biliary excretion of the unchanged drug is insignificant and renal excretion contributes only 10–35% of the delivered dose [2]. Furthermore, patients with impaired liver function display a significant reduction in the clearance of free (unbound) etoposide [11].

Etoposide is a drug with a low hepatic extraction ratio (ER_H). The hepatic blood flow ($Q_{H,tot}$) is about 1350 ml/min ($800\,ml\,min^{-1}\,m^{-2}$), corresponding to $475\,ml\,min^{-1}\,m^{-2}$ for plasma [6], whereas the body clearance (Cl_{tot}) of etoposide is $20\,ml\,min^{-1}m^{-2}$. since hepatic clearance of etoposide (Cl_H) contributes at most 70% of the Cl_{tot} (viz., Cl_{tot}-Cl_{renal}) [6], the Cl_H will not be higher than $14\,ml\,min^{-1}\,m^{-2}$ and, thus, the ER_H is at best $14/475 = 0.029$. This finding suggests a negligible role in the uptake of etoposide into hepatocytes for the albumin receptor [12] or any other carrier-mediated transport system. Since the ER_H is below the expected f_u (0.043), changes in the f_u result in proportional changes in ER_H and Cl_H [6]. The drug ($125\,mg/m^2$) has been infused into the hepatic artery within 1 h, resulting in a dose rate of $2\,mg\,min^{-1}\,m^{-2}$. The blood flow through the hepatic artery ($Q_{H,art}$) is $175\,ml\,min^{-1}\,m^{-2}$, corresponding to $100\,ml\,min^{-1}\,m^{-2}$ for plasma. Consequently, the maximal plasma level of etoposide in the hepatic artery (at the end of the infusion) is about 35 – 40 mg/l (viz., the sum of 20 mg/l plus the drug's C_{max} in the systemic circulation), which is only about 2 times higher than that achieved after i.v. administration. In a study in patients receiving ablative chemotherapy, including a very high dose (up to $2400\,mg/m^2$) of etoposide, plasma levels in the range of 100 –200 mg/l have been observed without evidence of nonlinear pharmacokinetics [7]. Assuming that extraction from the hepatic arterioles is as effective as that from the portal venules, this finding indicates that a saturation of hepatic elimination probably will not occur at 35– 40 mg/l.

Since in HAI the drug is given just before this major eliminating organ, we anticipated that this might have an effect on the pharmacokinetics of etoposide. The establishment of an equilibrium between free and bound drug is a time-dependent process, and if HAI would lead to the presentation of an increased fraction of free drug to the liver, this should result in an increased drug extraction ratio and, thus, to a reduced systemic drug bioavailability. For example, if the f_u of etoposide in the hepatic arterioles during the HAI period would increase from 0.043 to 0.20, the $ER_{H,art}$ should likely increase from 0.029 to about 0.15, which would cause a reduction in the AUC of about 12%. Given the lack of a difference in the AUC values recorded after i.v. infusion and HAI, it is obvious that any change in the ER_H and, thus, in f_u would be much smaller. This indicates that under in vivo conditions the equilibrium between free and bound drug is established before etoposide reaches the vascular bed of the liver.

The clinical objective of HAI of etoposide is to gain a pharmacological advantage by an increase in local (free) drug exposure during a first pass of the liver, in resemblance to the intrapleural and intraperitoneal routes of administration. Although during the HAI period the drug exposure of tissues (including metastatic tumor in the liver) that depend upon perfusion by hepatic arterioles will be about 2 times higher, the overall exposure of the liver to drug is increased by only about 20% (viz., from 100 to $120\,mg\,l^{-1}\,h$). Since HAI of etoposide also does not lead to a substantially higher exposure to the free (active) drug, our results do not provide a pharmacokinetic rationale for the use of this more complex procedure of drug administration in the treatment of (metastatic) cancer located in the liver.

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