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Disposition of total and unbound etoposide following high-dose therapy*

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Abstract. Total and unbound etoposide pharmacokinetics were studied in 16 adult patients (median age, 34 years; range, 18–61 years) undergoing autologous bone marrow transplantation for advanced lymphoma after receiving high-dose etoposide (35–60 mg/kg) as a single intravenous infusion. Pretreatment values for mean serum albumin and total bilirubin were 3.0 ± 0.4 g/dl and 0.5 ± 0.4 mg/dl, respectively. Etoposide plasma concentrations and protein binding (%unbound) were determined by high-performance liquid chromatography (HPLC) and equilibrium dialysis, respectively. Pharmacokinetic parameters for unbound and total etoposide were calculated by nonlinear regression analysis using a two-compartment model. The mean ($\pm$SD) parameters for total etoposide included: clearance (CL), 31.8 ± 17.7 ml min^{-1} m^{-2}; volume of distribution (V_{ss}), 11.5 ± 5.9 l/m^2, and terminal half-life ($t_{1/2}\ \beta$), 7.2 ± 3.7 h. Mean unbound CL was 209.6 ± 62.7 ml min^{-1} m^{-2} and %unbound was $16\% \pm 5\%$. The mean etoposide %unbound was inversely related to serum albumin ($r^2 = 0.45$, $P = 0.0043$). The mean %unbound at the end of the etoposide infusion was higher than that at the lowest measured concentration (21% vs 13%, respectively; $P = 0.017$), suggesting that concentration-dependent binding may occur after high etoposide doses. The median total CL was higher in patients with serum albumin concentrations of ≤ 3.0 g/dl than in those with levels of >3.0 g/dl (34.6 vs 23.5 ml min^{-1} m^{-2}, $P = 0.05$). Total CL was directly related to %unbound ($r^2 = 0.61$, $P = 0.0004$). Unbound CL was unrelated to either serum albumin or %unbound. These results demonstrate that hypoalbuminemia is independently associated with an increased etoposide %unbound and rapid total CL after the administration of high-dose etoposide. Unbound CL in hypoalbuminemic patients is unchanged in the presence of normal total bilirubin values.

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Introduction

Autologous bone marrow transplantation (ABMT) after high-dose chemotherapy and/or chemoradiotherapy permits dose escalation of antineoplastic agents in an attempt to improve response rates and increase the likelihood of long-term disease-free survival [7]. Typically, marrow is infused at 2–3 days following the end of the preparative regimen. Because marrow infusion circumvents the problem of prolonged marrow suppression, the dose-limiting toxicity is confined to extramedullary tissues.

Etoposide has antineoplastic activity at conventional doses (e.g., 250–500 mg/m^2 given over 3–5 days) in a variety of hematologic malignancies and solid tumors. High-dose etoposide (up to 2.4 g/m^2 given over 3 days or 1–3 g/m^2 given as a single 4-h infusion) has been used in conjunction with total-body irradiation or chemotherapy as a preparative regimen prior to ABMT [5, 13, 22]. In the setting of ABMT, the dose-limiting nonhematologic toxicity of etoposide is stomatitis and mucositis [5, 22].

Knowledge of the pharmacokinetic behavior of high-dose etoposide is important in predicting drug disposition in patients with varying degrees of excretory organ function and in ensuring that the drug has been eliminated from the plasma prior to marrow infusion. Several studies of the elimination of total etoposide have shown that it follows first-order rate processes at doses as high as 3 g/m^2 [13, 19]. No report has been published that describes the elimination of unbound etoposide following high-dose therapy.

Etoposide is extensively protein-bound (mean %unbound, 4%) when measured in plasma from normal volunteers, but the %unbound has been shown to be increased (mean, $14\% \pm 10\%$) and highly variable (range, 6%–37%) when etoposide is given in conventional doses to patients with cancer [26]. These alterations in protein binding were significantly related to reductions in serum albumin and increases in total bilirubin and not to the malignant process per se [26]. Since only non-protein-bound drug is available to diffuse from the circulation and interact with receptors, an increase in the %unbound may result in enhanced antitumor activity and toxicity. Indeed, an in vitro study

showed that protein binding played an important role in modifying the response of bone-marrow progenitor cells to etoposide [2]. In a recent study, systemic exposure (area under the serum concentration-time curve) to unbound etoposide showed a better correlation with hematologic toxicity than did a model using total systemic exposure [27]. A recent in vitro study has demonstrated that etoposide exhibits concentration-dependent protein binding over a concentration range of 1–250 μg/ml [10]. This spectrum spans the range of plasma concentrations anticipated after most high-dose etoposide regimens. Thus, the capacity of albumin to bind etoposide may be exceeded, resulting in an even greater %unbound than that observed in cancer patients receiving conventional doses.

The present study was designed to evaluate the pharmacokinetics of total and unbound etoposide in adult patients receiving high-dose etoposide therapy. Relationships between pharmacokinetic parameters and patient-specific clinical and laboratory variables were also evaluated.

Patients and methods

Eligibility and treatment protocol. Patients in this protocol were participating in a study of high-dose busulfan and etoposide as a preparative regimen for ABMT. The clinical aspects of the study have been reported elsewhere [22]. The protocol was approved by the Protection of Human Subjects Committee of Montefiore University Hospital, and written informed consent was obtained from all patients.

Briefly, patients with relapsed and/or refractory Hodgkin's disease and non-Hodgkin's lymphoma were eligible. Patients were ineligible if they had received prior pelvic irradiation or showed evidence of lymphoma on bone marrow biopsy. Marrow was harvested at least 4 weeks after the last administration of myelosuppressive chemotherapy. Patients then received 4 consecutive days of oral busulfan (1 mg/kg q6h) followed by a scheduled 4-h intravenous infusion of etoposide (35–60 mg/kg actual body weight) on the next day. Etoposide was intended to be diluted in normal saline to a concentration of 0.1 mg/ml, but because crystallization occurred when the drug was given to the first patient in this manner, subsequent patients received undiluted etoposide through an Omniflow model 4000 (Omniflow, Inc.; Wilmington, Mass.) or a Travenol model AS20S (Travenol Laboratories, Inc.; Hookset, N.H.) infusion pump. Patients also received oral phenytoin (300 mg daily) beginning on the day prior to the first busulfan dose and continuing for a total of 5 or 6 days. Allopurinol (300 mg daily) was begun on the day prior to the first busulfan dose and continued for a total of 6 days. A rest period of 64–72 h was scheduled between the end of the etoposide infusion and marrow infusion. The rest period could be extended if interim pharmacokinetic analysis predicted total plasma etoposide concentrations of >0.3 μg/ml at the scheduled time of marrow infusion. A target concentration of ≤0.3 μg/ml had previously been shown by in vitro studies in our laboratory to produce minimal inhibition of growth (≤22%) in a colony-forming unit assay and was considered to be a safe level for marrow infusion [24].

Sample collection and drug analysis. Blood samples were collected in heparinized tubes before the etoposide infusion, midway through the infusion, at the end of the infusion, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, and 60 h after the completion of the infusion. Samples were centrifuged, and plasma was separated and frozen at –20°C until analysis. Samples were extracted using a liquid-liquid extraction process, and plasma concentrations of etoposide were measured by high-performance liquid chromatography (HPLC) with ultraviolet detection [9]. This method was determined to be precise (intraday and interday coefficient of variation, from 0.8% to 4.8%) and accurate (mean prediction error, –0.03 to –3.1) over a range of etoposide concentrations of 0.55 to 45 mg/ml, with the limit of sensitivity being 0.05 μg/ml. Samples that were above the upper limit of the calibration curve were diluted with blank plasma and then extracted and assayed as usual.

Etoposide protein-binding methodology. Etoposide protein binding was determined in all samples for which an adequate volume of plasma (i.e., ≥ 1 ml) was available (>90% of samples). The percentage of unbound (%unbound) etoposide in each plasma sample analyzed for total etoposide was determined using an equilibrium dialysis technique with tritiated etoposide [10]. Tritiated etoposide was obtained from Moravek Biochemical (Brea, Calif.) and had a specific activity of 1 Ci/mmol. The radiochemical purity of the radiolabeled etoposide was determined by liquid scintillation counting of fractions following HPLC [25]. The radiochemical purity of etoposide used in this study was >96%. Plasma samples were dialyzed against an equal volume of Sorensen's buffer at pH 7.4 and 37°C for 6 h.

The etoposide %unbound was calculated from the ratio of the disintegrations per minute of [^{3}H]-etoposide in the buffer to the disintegrations in an aliquot of plasma using an external standardization method for quench correction. The correction for volume shift was made by the method of Huang [15]. Correction for radiochemical purity was carried out by the method of Bjornsson et al. [4]. The etoposide binding ratio (ratio of molar concentrations of bound drug to free drug, BR) was calculated from the equation BR = (1/fraction unbound)–1.

Pharmacokinetic analysis. The unbound etoposide concentration (C_u) was determined from the product of the etoposide %unbound measured in that sample and the total etoposide concentration (C_u = %unbound$_i$ × C_{t_i}). In an iterative approach, a two-compartment open model was fit to each patient's etoposide concentration-time data using maximal likelihood [6]. The mean and standard deviation of these parameter estimates were then used as population priors for a Bayesian estimation with ADAPT II software [6]. The parameters estimated included the volume of the central compartment (V_c), distribution rate constants (K_{cp} and K_{pc}), and the elimination rate constant (K_{el}). The parameters clearance (CL), terminal half-life ($t_{1/2\,\beta}$), and volume of distribution at steady state (V_{ss}) were calculated [11].

Statistical analysis. Statistical analyses were performed with the SAS statistical package [23]. The a priori level of significance for all statistical tests was $P \leq 0.05$. Data are reported as mean values ± SD unless otherwise noted. Simple linear and/or multiple stepwise regression analyses were used to evaluate relationships between total and unbound etoposide pharmacokinetic parameters versus clinical and biochemical variables. The patient-specific variables used in the analysis were age, gender, weight, body surface area, serum creatinine, creatinine clearance, serum albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and lactic dehydrogenase (LDH). Laboratory values were obtained on or nearest to the day of etoposide infusion.

Results

A total of 16 patients were studied, including 13 men and 3 women whose median age was 34 years (range, 18–61 years). Demographic and laboratory characteristics of the patient population are summarized in Table 1. Seven patients had Hodgkin's disease and nine patients had non-Hodgkin's lymphoma. All patients had received prior treatment with radiation and/or various chemotherapy regimens.

The total etoposide dose for each patient ranged from 2.75 to 4.55 g (35–60 mg/kg) infused over a median of 4.4 h (range, 3.4–7.3 h). The mean period between the end of the etoposide infusion and marrow infusion was 81 ± 19 h (range, 64–138 h). As determined by log-linear ex-

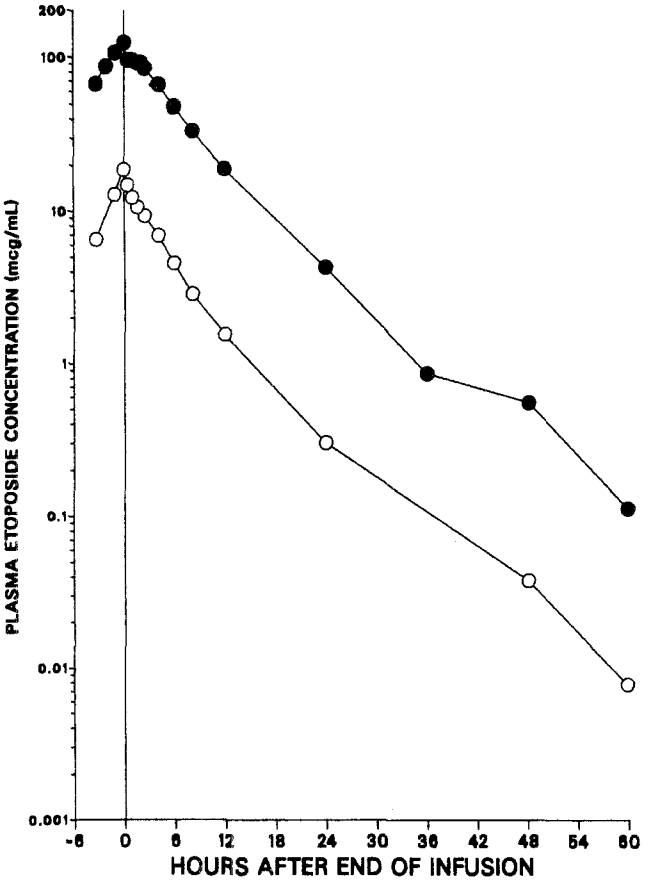

Fig. 1. An individual (patient 13) concentration-time curve generated for total (*filled circles*) and unbound (*open circles*) etoposide after the infusion of 60 mg/kg by 4-h intravenous infusion

trapolation using the last several concentration-time points, the estimated plasma etoposide concentration at the actual time of marrow infusion was 0.050 ± 0.081 μg/ml (range, <0.001–0.294 μg/ml).

A concentration-time curve generated for total and unbound etoposide in an individual patient is shown in Fig. 1. Concentrations of total and unbound etoposide peaked at the end of the infusion and declined in a parallel log-linear fashion thereafter. Mean etoposide pharmacokinetic parameters for total and unbound drug are presented in Table 2.

The number of protein-binding determinations within a patient course varied from 11 to 19. The intrapatient coefficient of variation for etoposide %unbound ranged from 17% to 45% over the dosing interval studied. Excellent agreement between the median and mean values within patients was observed (r = 0.95; slope, 0.84), such that either value could be used as the representative value for an individual patient. The mean etoposide %unbound was $16\% \pm 5\%$ (range, 10%–26%), and the corresponding mean binding ratio was 5.6 ± 1.9 (range, 2.8–9.0).

In an evaluation of the effect of variable albumin concentrations on etoposide protein binding, linear regression analysis revealed a significant relationship between the etoposide binding ratio and serum albumin (r^2 = 0.33, P = 0.02). As determined by simple linear regression analysis, %unbound was inversely related to serum albumin (r^2 = 0.45, P = 0.0043; Fig. 2).

The mean ($\pm$SD) etoposide concentrations at the completion of the infusion and at the lowest measured concentration were 120 ± 47 and 4 ± 7 μg/ml, respectively. The mean %unbound was significantly higher at the end of the infusion (21%) than at the lowest measured concentration (13%; P = 0.017, paired t-test).

As determined by simple linear and multiple stepwise regression analysis, the mean V_{ss} was related only to serum albumin (r^2 = 0.64, P = 0.0002) and was unrelated to age,

Table 1. Demographic and laboratory characteristics

Patient number	Age (years) gender	Total bilirubin (mg/dl)	Alkaline phosphatase (IU/l)	Serum albumin (g/dl)	Serum creatinine (mg/dl)	Creatinine clearance (ml/min)
1	49/M	0.5	264	3.2	0.8	89
2	52/M	0.6	107	3.5	1.1	90
3	46/F	0.2	100	2.7	0.5	90
4	24/M	0.4	138	3.0	0.5	–[a]
5	35/M	0.2	96	3.3	0.7	248
6	34/M	0.3	95	2.9	0.9	62
7	34/M	0.4	232	2.7	1.2	–[a]
8	39/F	0.8	426	3.3	0.8	70
9	51/M	1.7	136	2.4	0.6	–[a]
10	34/M	0.4	355	2.0	0.6	134
11	61/F	0.4	111	3.5	0.6	62
12	19/M	0.8	277	2.8	0.5	83
13	21/M	0.3	154	3.2	1.1	112
14	18/M	0.3	76	3.4	0.5	136
15	28/M	0.3	95	3.3	1.2	36
16	29/M	0.5	109	3.3	0.8	–[a]
Mean	36	0.5	173	3.0	0.8	101
SD	13	0.4	102	0.4	0.2	52
Normal range		0.2–1.2	30–115	3.0–5.5	0.7–1.5	>60

[a] Creatinine clearance not measured

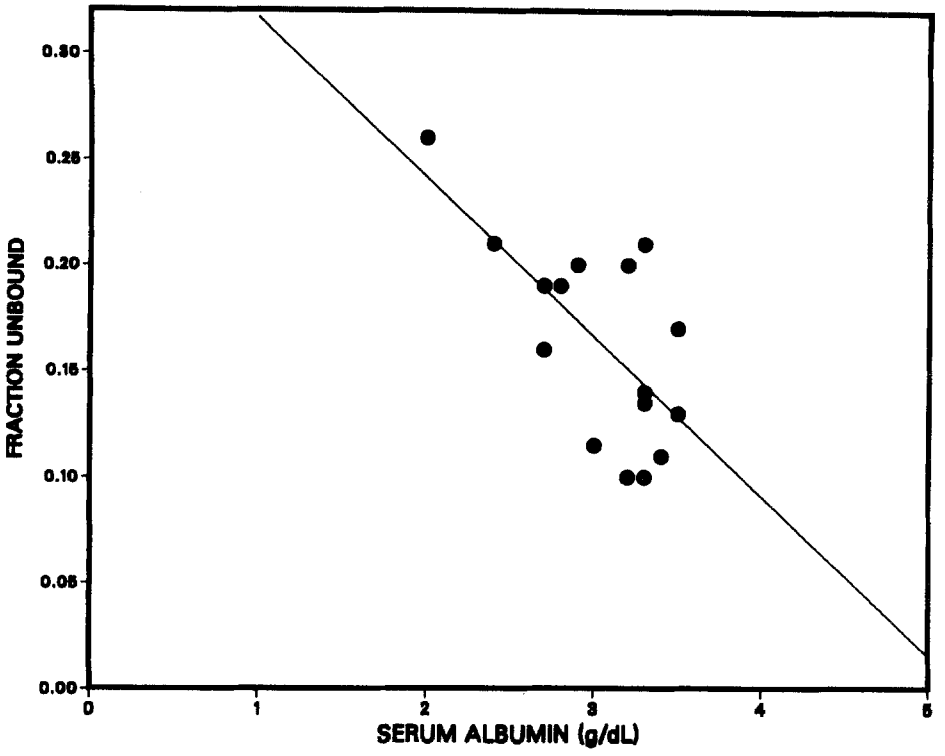

Fig. 2. Relationship between the unbound etoposide fraction and serum albumin

Table 2. Mean (±SD) etoposide pharmacokinetic parameters[a]

Variable	Total etoposide	Unbound etoposide
Intercompartmental rate constants (h^{-1})		
K_{cp}	1.52±1.55	0.07±0.03
	(0.01–5.44)[b]	(0.03–0.14)
K_{pc}	0.38±0.21	0.16±0.06
	(0.04–0.88)	(0.09–0.27)
Volume of distribution (l/m^2)		
V_c	3.4±1.9	46.1±16.5
	(0.6–7.0)	(20.5–80.3)
V_{ss}	11.5±5.9	66.7±20.3
	(2.5–29.2)	(35.5–108.1)
Clearance (ml min^{-1} m^{-2})	31.8±17.7	209.6±62.7
	(13.7–88.1)	(115.5–376.8)
Half-life (h)		
Distribution ($t_{1/2\alpha}$)	0.7±0.9	1.8±0.4
	(0.1–3.4)	(1.4–2.6)
Terminal ($t_{1/2\beta}$)	7.2±3.7	7.1±2.5
	(3.8–19.4)	(4.3–12.2)
End-of-infusion concentration (μg/ml)	119.6±47.3	22.5±9.7
	(35.5–192.0)	(11.3–54.3)
AUC_{0-inf} (μg h ml^{-1})	1273±561	168±49
	(321–2320)	(75–264)

[a] K_{cp}, Rate of drug transfer from the central to the peripheral compartment; K_{pc}, rate of drug transfer from the peripheral to the central compartment; V_c, volume of the central compartment; V_{ss}, volume at steady state; AUC_{0-inf}, area under the plasma concentration-time curve from time zero to infinity

[b] Range

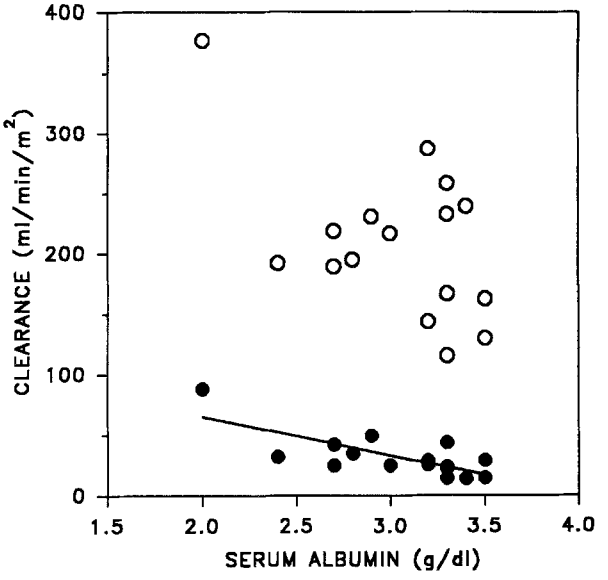

Fig. 3. Relationship between total (*filled circles*) and unbound (*open circles*) etoposide clearance versus serum albumin

gender, weight, or other laboratory parameters. No significant relationship was observed between the etoposide dose and the total or unbound CL, V_{ss}, or K_{el}.

Both total and unbound etoposide CL were unrelated to age, gender, weight, renal function, or liver-function tests. Total CL was inversely related to serum albumin ($r^2 = 0.53$, $P = 0.0013$), whereas unbound CL was not related to serum albumin (Fig. 3). The median total CL in patients with serum albumin concentrations of ≤3.0 g/dl was 34.6 ml min^{-1} m^{-2} as compared with 23.5 ml min^{-1}

m^{-2} in patients with albumin levels of >3.0 g/dl ($P = 0.05$, Mann-Whitney U-test). Unbound CL did not significantly differ between the two groups. Total CL was directly related to %unbound ($r^2 = 0.61$, $P = 0.0004$), but unbound CL was unrelated to %unbound.

Discussion

Few studies have evaluated the pharmacokinetics of etoposide used at high doses in conjunction with bone marrow transplantation [13, 19]. None of these studies has evaluated etoposide protein binding, which has been shown to be reduced after conventional doses in cancer patients with hypoalbuminemia and/or hyperbilirubinemia. Reduced serum albumin concentrations offer fewer binding sites for etoposide, whereas hyperbilirubinemia may result in displacement of the drug from those binding sites [28]. The administration of high-dose etoposide poses the additional potential for saturation of protein-binding sites and a further increase in %unbound [16], which may result in increased nonmyeloid toxicity or decreased probability of successful engraftment in bone-marrow transplant patients.

The etoposide %unbound found in the present study (mean, 16% ± 5%) was similar to that determined in cancer patients treated with conventional-dose etoposide (mean, 14% ± 10%) [26]. In the previous study, the reduction in protein binding was primarily related to hypoalbuminemia and hyperbilirubinemia rather than to the malignancy per se, as direct relationships were reported between the binding ratio and serum albumin and between %unbound and total bilirubin [26]. Furthermore, the cancer patients with albumin levels of ≥ 4 g/dl had a mean %unbound (7%) that was similar to that of the normal volunteers (4%).

Patients in our study population differed from those described above in that mean bilirubin values were relatively normal (0.5 ± 0.4 mg/dl) as compared with those found in the hyperbilirubinemic group in the earlier study (mean, 3.2 ± 4.8 mg/dl). Consequently, we found no correlation between %unbound and total bilirubin. Our patients did have substantial hypoalbuminemia (range, 2.0 to 3.5 g/dl), and a significant linear correlation between the binding ratio and serum albumin was observed. Because of these differences in biochemical variables from previous studies, the effect of a reduced albumin concentration on protein binding, total CL, and unbound CL could be evaluated independently of changes caused by marked hepatic dysfunction and/or hyperbilirubinemia.

The mean total etoposide CL observed in our patients (31.8 ± 17.7 ml min^{-1} m^{-2}) was greater than that previously reported for patients receiving conventional doses of etoposide (18.7 ± 5.5 ml min^{-1} m^{-2}) [28] or high-dose etoposide plus total-body irradiation (24.6 ± 6.8 ml min^{-1} m^{-2}) [19]. These discrepancies may have been due to differences between the study populations with respect to the degree of hypoalbuminemia, hyperbilirubinemia, and protein binding. In our study, patients with serum albumin concentrations of ≤ 3.0 g/dl had significantly greater total etoposide CL than those whose albumin levels were >3.0 g/dl. Other investigators have observed the same relationship using conventional doses of etoposide [1, 28]. In the present study, total CL was also directly related to %unbound. Thus, low albumin concentrations result in a higher unbound fraction (F_u), making more free drug available for elimination and increasing total CL (i.e., $CL = F_u \times CL_{INT}$) [16]. Although serum albumin concentrations were not reported by Newman et al. [19], the mean albumin levels obtained in the present study (3.0 ± 0.4 g/dl) were somewhat lower than those found in other studies (3.3 ± 0.4 g/dl [1] and 3.4 ± 0.4 g/dl [28]) reporting CL values slightly lower than those determined in our study. Lower mean serum albumin levels along with relatively normal bilirubin values may have accounted for our observed increase in total CL.

The unbound CL observed in our patients (209.6 ± 62.7 ml min^{-1} m^{-2}), who had relatively normal bilirubin levels, was similar to that reported by Stewart et al. [28] after conventional doses (220 ± 90 ml min^{-1} m^{-2}) in patients with normal total bilirubin levels (<1.0 mg/dl). Also, unbound CL was independent of %unbound in our study. These results provide evidence that hypoalbuminemia alone is associated with a considerable increase in %unbound, a high total CL, and a normal unbound CL if hepatic intrinsic CL is not markedly altered by liver disease.

It is possible, albeit unlikely, that the slightly higher free fraction observed in our study relative to previous work in patients with cancer resulted from competition for plasma protein-binding sites by coadministered drugs such as phenytoin and busulfan. Phenytoin is approximately 90% protein-bound, almost exclusively to albumin, [20] but has been shown to cause negligible increases in the unbound fraction of other drugs because its molar concentration is very low at therapeutic plasma concentrations relative to that of albumin [18]. The extent of busulfan binding is unknown, but its short elimination half-life (approximately 2.5 h) [8] makes it unlikely that a substantial effect on etoposide binding would occur 24 h after the administration of the last busulfan dose.

It is also possible that differences in study design and concomitant drugs may have contributed to the difference between the CL values obtained in the two studies. Prior to etoposide administration, all patients in this study received seizure prophylaxis with oral phenytoin for 5 or 6 days to prevent seizures from high-dose busulfan [12, 17]. Holthuis et al. [14] reported an increased CL in one patient receiving concurrent etoposide and phenytoin (26.0 ml min^{-1} m^{-2}) as compared with the mean value for the remainder of the study population (17.7 ml min^{-1} m^{-2}). Phenytoin has also been shown to increase the CL of teniposide, which is structurally similar to etoposide [3]. Increased teniposide CL has been associated with a reduced oncolytic response [21]. Thus, a potential drug interaction between phenytoin and etoposide may also be of clinical significance and warrants further study.

In vitro studies have shown that etoposide exhibits concentration-dependent binding over a concentration range of 1–250 μg/ml [10]. Although our study was not designed to evaluate this phenomenon, the mean etoposide %unbound measured at the end of the infusion (21%) was significantly higher than that observed at the lowest measured concentration (13%). These findings are consistent with the re-

sults obtained in the previous in vitro study and suggest that concentration-dependent protein binding may occur at etoposide concentrations that are achievable after the administration of etoposide doses of 50–60 mg/kg.

In summary, hypoalbuminemia was independently associated with an increased unbound etoposide fraction and a rapid total CL. This effect occurred in the absence of meaningful increases in bilirubin concentrations. On the basis of these pharmacokinetic considerations, altered dosing is not warranted in patients with hypoalbuminemia and normal total bilirubin values since unbound CL is unchanged. However, dose reduction may be advisable in patients with a combination of hypoalbuminemia and liver disease.

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