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Use of etoposide in patients with organ dysfunction: pharmacokinetic and pharmacodynamic considerations

Clinton F. Stewart[1, 2]

[1] Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee, USA
[2] The Center for Pediatric Pharmacokinetics and Therapeutics, University of Tennessee, Memphis, Tennessee, USA

Abstract. Etoposide is a podophyllotoxin deriverative with activity against a wide variety of malignancies. It is also used in many clinical conditions in which renal or hepatic function is impaired. To establish a basis for making initial dose adjustments in patients with renal or hepatic dysfunction, the clinical pharmacology (e.g., absorption, distribution, protein binding, metabolism, and elimination) of etoposide is presented. Studies of the use of etoposide in patients with renal or hepatic dysfunction are summarized. The importance of protein binding to etoposide disposition, especially in patients with hepatic dysfunction is discussed. Pharmacodynamics refers to the relationship between drug concentration at the site of action (receptor) and pharmacologic response (toxicity or efficacy). The pharmacodynamics of etoposide has been studied in only a few patients with renal and (or) hepatic dysfunction and must be studied in larger populations before definitive dosing guidelines can be recommended. However, some general initial dosing recommendations for the use of etoposide in patients with renal and hepatic dysfunction are presented.

Key words: Etoposide – Pharmacokinetics – Pharmacodynamics

Introduction

Treatment of a cancer patient with therapeutic intent presumes a knowledge of the toxicity and efficacy of the drugs used. Ideally, the oncologist will want to minimize the probability of toxicity and maximize the probability of obtaining the desired therapeutic effect. Administration of any drug is a function of many variables, including dose, schedule, and route. Once the drug has been given to the patient, significant differences in its disposition exist between and, in some cases, within individuals. Knowledge of the pharmacokinetics of a drug can provide the oncologist with important information about this variability that can then be used to optimize drug administration [37].

As indicated in Table 1, etoposide has shown antitumor activity in many neoplastic disorders when given both as a single agent and in combination with other anticancer drugs [14]. Frequently patients receiving etoposide have altered and changing renal and (or) hepatic function due to the primary malignancy (e.g., hepatic metastases), comorbid disease (e.g., hepatitis, renal failure), other nephrotoxic drugs (e.g., aminoglycosides, amphotericin), and (or) other anticancer drugs used in combination with etoposide (e.g., cisplatin) [8, 10]. In the setting of altered organ function, additional variability in the disposition of etoposide may be observed.

The disposition of etoposide in patients with normal renal and hepatic function has been extensively studied; however, reports of etoposide pharmacokinetics in patients with renal and hepatic dysfunction are limited [1, 12, 21, 40]. Even fewer reports describe the pharmacodynamics of etoposide in this patient population [46]. Most published studies of etoposide pharmacokinetics have reported only the disposition of total etoposide, ignoring the variability inherent in the disposition of a drug that is highly protein-bound (i.e., >90%).

The reported schedule dependency of etoposide makes it likely that a knowledge of its clinical pharmacokinetics and pharmacodynamics will be relevant to patient care. This review summarizes the clinical pharmacology of etoposide; describes the use of etoposide in patients with renal and

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Correspondence to: C. F. Stewart, St. Jude Children's Research Hospital, P. O. Box 318, Memphis, TN 38101-0318, USA

Table 1. Etoposide-sensitive malignancies

Single-agent activity:
Small-cell lung cancer
Testicular carcinoma
Kaposi's sarcoma
Non-Hodgkin's lymphoma
Combination with cisplatin:
Small-cell lung cancer
Testicular carcinoma

hepatic dysfunction, focusing on the role of pharmacokinetics and pharmacodynamics; and provides dosing guidelines for etoposide use in this patient population.

Clinical pharmacology of etoposide

Oral absorption of etoposide formulated as a liquid-filled gelatin capsule is incomplete and erratic, with bioavailability in a small number of patients reported to range from 17% to 137% [7, 11]. Besides the substantial interpatient variability reported, intrapatient coefficients of variation for etoposide bioavailability have ranged from 16% to 53% [7]. Recently, Hande and colleagues [22] reported an effect of dose on etoposide bioavailability (i.e., 76% bioavailability for 100 mg/m^2 doses vs 48% for 400 mg/m^2; $P < 0.01$). The disposition of etoposide after oral administration is similar to that observed after intravenous administration [48].

The mean volume of distribution at steady state (Vd_{ss}) ranges from 4.7 to 15.7 l/m^2. Etoposide has been reported to have poor penetration into cerebrospinal fluid (CSF) following the administration of standard and high doses (e.g., <2% of the serum concentration; CSF concentrations of 0.1–1.4 μg/ml) [18, 24]. Nonetheless, objective responses have been observed after the administration of high-dose etoposide in patients with brain metastases. In vitro plasma protein-binding experiments showed that the etoposide free fraction in plasma from cancer patients was 13.9% as compared with 4.3% in plasma from healthy volunteers [43]. Etoposide is bound primarily to albumin; however, one study has suggested that it might also bind to alpha-1 acid glycoprotein [15]. Etoposide protein binding displays marked species and, in the case of mice, interstrain variability [16]. The etoposide fraction unbound was greater in all animal species studied than in humans and was highest in sheep plasma (0.66 ± 0.001 vs 0.049 ± 0.001 in human plasma). In both in vitro and in vivo studies, high concentrations of bilirubin increase the percentage of etoposide unbound. On the basis of in vitro studies, it is likely that bilirubin displaces etoposide from common binding sites on albumin [15].

A proposed metabolic schema for etoposide is depicted in Fig. 1. Metabolites identified thus far include the hydroxy acid derivatives, cis-(picro) lactone, aglycone glucuronides, and the glucuronide and sulfate conjugates of the parent drug [9, 13, 19]. In reports published thus far, etoposide metabolites recovered in the bile and urine of animals or humans have amounted to less than 10% of the delivered dose [1, 21]. The results of an ongoing study using stable labeled etoposide will provide definitive data concerning the biliary disposition of etoposide. More recent work with human microsomes has revealed that O-demethylation of the dimethoxyphenolic pendant ring of both teniposide and etoposide by cytochrome P450 enzymes leads to formation of the catechol metabolite [38]. Although the quantitative significance of the formation of this metabolite as an elimination pathway is unknown, it may have clinical significance if the catechol is cytotoxic in vivo.

Approximately 50% of a delivered dose is recovered in the urine within 24 h as unchanged etoposide and etoposide glucuronide (range, 20%–81%) [11, 12]. Fecal elimination may account for up to 16% of the dose; however, most investigators report biliary excretion to be minimal (<2%) [1]. Thus, recovery of etoposide is incomplete. A significant amount of the etoposide dose remains unaccounted for, and the effect that altered renal or hepatic function has on this is unknown.

Depending on the assay methodology, the mean terminal half-life in adult cancer patients has ranged from 4 to 8 h and is not related to the etoposide dose. In adult cancer patients with normal renal and hepatic function the mean etoposide systemic clearance ranges from 16 to 39.3 ml min^{-1} m^{-2} and is independent of the dose over a wide dose range (80–3500 mg/m^2) [14].

Recent clinical studies have reported data to support early in vitro observations of a concentration-effect relationship for etoposide. In two human tumor cell lines, MOLT (T-cell lymphoma) and 9812 (bronchogenic carcinoma), cell cytotoxicity increased as etoposide concentration and duration of exposure increased [50]. Following a 72-h continuous etoposide infusion, Bennett and associates [2] showed a relationship between drug exposure ("systemic exposure") and myelosuppression. More recently, other investigators have reported a mathematical relationship between etoposide systemic exposure and toxicity that could be modeled by an E_{max} model [30, 33, 46].

Whereas many workers have reported the relationship between systemic exposure and toxicity, only recently has the relationship between efficacy and systemic exposure to the epipodophyllotoxins been reported [39]. The use of prolonged low-dose oral etoposide has shown significant activity in small-cell lung cancer, presumably due to prolonged exposure to low etoposide plasma concentrations [42]. Preliminary reports from a study of continuous-infusion etoposide designed to maintain plasma concentrations between 1 and 3 μg/ml suggest that antitumor effects can be achieved without the myelosuppression observed in other schedules with higher peaks (i.e., >3 μg/ml) [17].

Use of etoposide in patients with renal dysfunction

Much has been published regarding drug use in patients with renal dysfunction, and it is widely recognized that giving usual doses of some drugs to patients with renal insufficiency can lead to untoward effects [3, 27, 47]. Table 2 provides specific examples of causes of renal dysfunction in patients with cancer. Although many factors

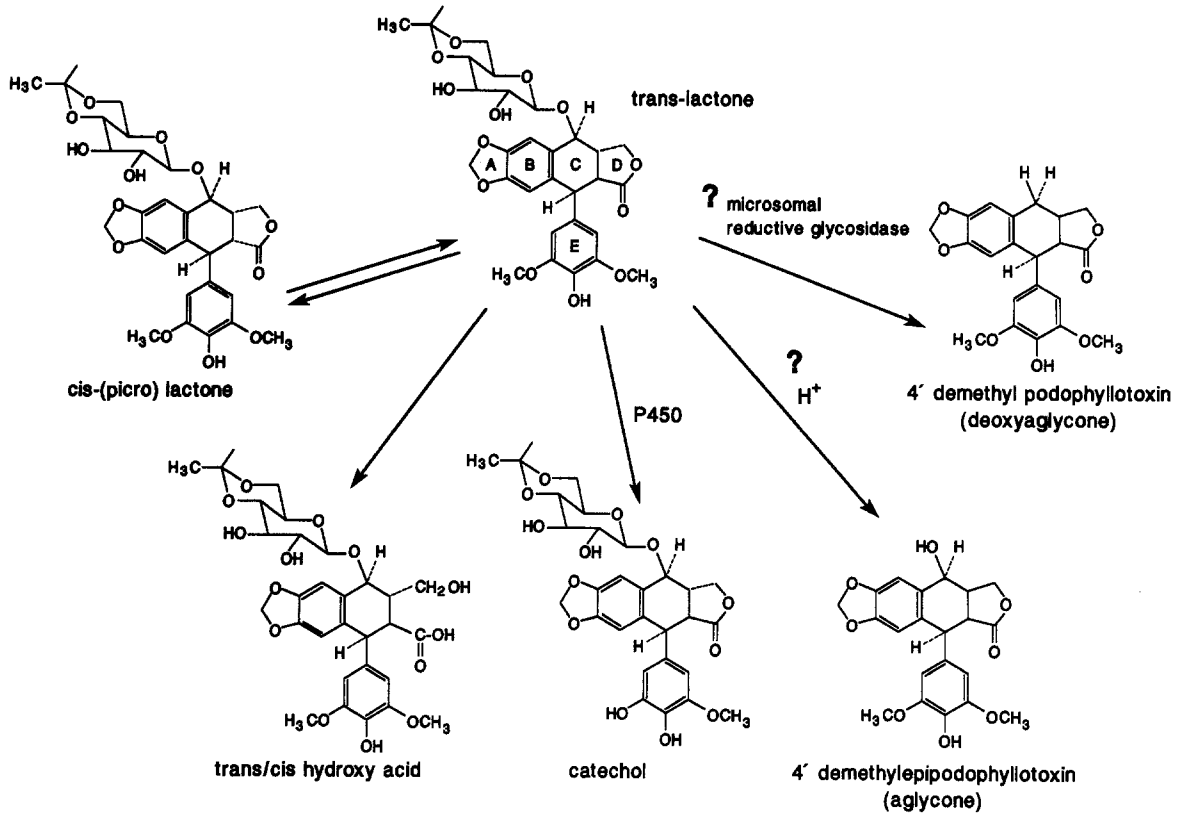

Fig. 1. Metabolic schema for etoposide

may lead to diminished renal function in the patient with cancer, few studies have specifically evaluated the effect of renal dysfunction on the disposition of anticancer drugs.

For many drugs, dose adjustment in patients with renal dysfunction is based on an estimate of remaining renal function (e.g., serum creatinine, creatinine clearance) and a mathematical relationship between renal function and a pharmacokinetic parameter such as clearance [26]. Usually these mathematical relationships have been determined in population studies of patients with normal renal function, not in patients with renal dysfunction. Renal dysfunction may also affect other aspects of drug disposition (absorption, distribution, metabolism, and elimination), not just clearance.

This situation is further complicated because routine measures of remaining renal function (e.g., serum creatinine, creatinine clearance) do not always accurately reflect the underlying renal function, especially the ability of the kidney to clear drugs [28, 29, 49]. Moreover, since renal function may not be stable, these measures of renal function often lag behind. A factor often not considered is the effect that uremic toxins may have on the pharmacodynamic target (e.g., bone marrow). Thus, studies of etoposide disposition in patients with renal dysfunction are essential for appropriate dose adjustment.

D'Incalci and colleagues [12] studied 18 patients with normal renal and hepatic function and 8 patients with renal dysfunction [serum creatinine, >1.5 mg/dl (range, 1.5–11.0 mg/dl); creatinine clearance, <43 ml/min (range, 4–43 ml/min)]. Etoposide systemic clearance was significantly lower and the volume of distribution and terminal half-life were significantly greater in patients with renal dysfunction as compared with the control group (see Fig. 2). The percentage of the dose excreted in the urine as etoposide or etoposide glucuronide was lower in the patients with renal dysfunction. Etoposide clearance was highly correlated ($r = 0.86$, $P < 0.001$) with creatinine clearance (see Fig. 3). Toxicities were not compared between the two groups since most patients received or had received other anticancer drugs, complicating the interpretation of the comparison. Although etoposide clearance was lower in the patients with renal dysfunction, the authors did not provide dose recommendations for patients with renal dysfunction.

Table 2. Causes of renal dysfunction in patients with cancer

Direct tumor invasion:
Parenchymal involvement (primarily leukemias, lymphomas)
Ureteral obstruction
Toxic tumor metabolites:
Uric acid
Paraproteins
Toxic anticancer drug therapy:
Methotrexate
Cisplatin
Streptozotocin
Ifosfamide
Nitrosoureas
Tumor-associated glomerulonephritis
Severe vomiting and dehydration

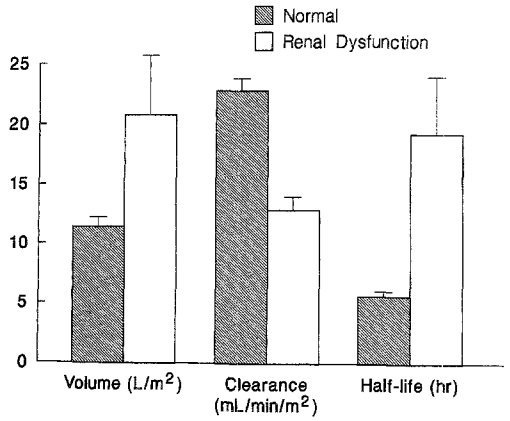

Fig. 2. Bar graph of etoposide pharmacokinetic parameters in normals as compared with patients with renal dysfunction (data from D'Incalci et al [12])

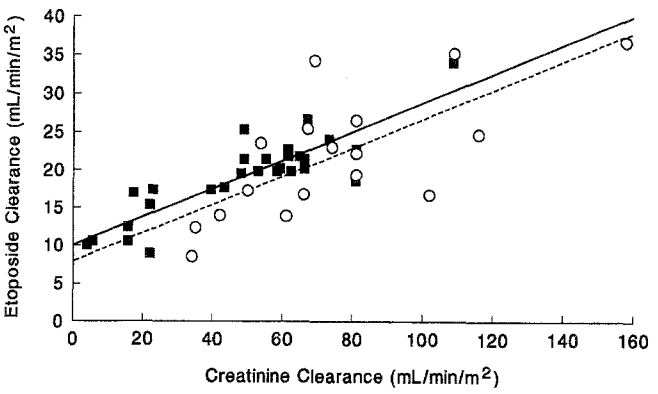

Fig. 3. Scatterplot of total etoposide systemic clearance versus creatinine clearance (*Filled squares* data from D'Incalci et al [12], *open circles* data from Arbuck et al [1])

Arbuck and colleagues [1] studied 17 patients, some with moderate renal dysfunction (serum creatinine range, 0.5–1.7 mg/dl; creatinine clearance range, 34–158 ml min^{-1} 1.73 m^{-2}). No difference was observed in pharmacokinetic parameters (clearance, Vd_{ss}, beta half-life) in eight patients with a creatinine clearance of $\geq$70 ml min^{-1} 1.73 m^{-2} and nine patients with a creatinine clearance of $<$70 ml min^{-1} 1.73 m^{-2}. In a linear regression analysis of liver and renal function tests and patient-specific variables, etoposide clearance was predicted by creatinine clearance ($r^2 = 41\%$), with the next strongest predictor, albumin, improving the r^2 value to 57%.

The pharmacokinetics and myelosuppressive effects of single-agent etoposide (500 mg/m^2 given over either 5 or 8 days) were evaluated in 45 patients with normal renal function, 9 patients with serum creatinine levels ranging from 1.1 to 1.4 mg/dl, and 6 patients with serum creatinine values of $>$1.4 mg/dl [25]. All patients had normal hepatic function. Patients with elevated levels of serum creatinine ($>$1.4 mg/dl) had significantly altered etoposide pharmacokinetics and significantly lower nadir WBC, neutrophil, and platelet counts than patients with normal serum creatinine values. These investigators suggested a 30% decrease in the etoposide dose for patients with normal hepatic function and serum creatinine levels of $>$1.4 mg/dl.

Pfluger and colleagues studied etoposide pharmacokinetics in 35 patients (15 patients previously reported [34]), most of whom had normal renal and hepatic function [35]. Pharmacokinetic parameters (clearance, volume, and half-life) were correlated with patient-specific demographic and biochemical measurements. Renal impairment (serum creatinine, $>$1.2 mg/dl), prior therapy with cisplatin, and age were associated with significant alterations in etoposide pharmacokinetics (e.g., decreased clearance and increased area under the plasma concentration-time curve, AUC). Patients that had received prior cisplatin therapy had on average a 30% reduction in etoposide systemic clearance; however, the authors did not provide details about the timing or administration of the prior cisplatin.

Thus far, only the effect of long-term renal dysfunction on etoposide disposition has been considered; however, the potential for acute changes in renal function altering etoposide disposition must also be considered (e.g., coadministration of etoposide with cisplatin even in the patient with "normal" serum creatinine or creatinine clearance).

Use of etoposide in patients on hemodialysis

Holthuis et al. [23] studied a patient with chronic renal failure who was treated with short-infusion etoposide 2 h after a hemodialysis session. They reported no difference in the Vd_{ss}, clearance, or terminal half-life as the dose of etoposide was increased from 38 to 102 mg/m^2 on four successive courses. However, as the dose was increased on the fifth course to 127 mg/m^2, the Vd_{ss} increased by 50%, the clearance remained unchanged, and the terminal half-life doubled. The authors attributed this observation to saturation of plasma protein binding. The patient was dialyzed three times a week for 4 h with a single-needle double-headed pump system. A plate dialyzer with a Cuprophane membrane (11 μm thick; effective surface area, 1.35 m^2) was used, and the blood flow and dialysate flow were 300 and 500 ml/min, respectively. No etoposide was found in the dialysate or adsorbed to the dialysis membrane.

Brindley et al. [5] measured etoposide concentrations before and after hemodialysis in one patient who received 100 and 160 mg etoposide before hemodialysis. Details were not provided about the actual dialysis procedure. Etoposide serum concentrations were higher at 21–31.5 h after dosing with 100 mg than in patients with normal renal function receiving 100 mg/m^2. As observed by Holthuis et al. [23], hemodialysis did not decrease the etoposide serum concentration, presumably due to high plasma protein binding.

Use of etoposide in patients with hepatic dysfunction

Although etoposide is largely renally excreted (50%), there is a significant nonrenal component to its elimination from the body. Of this nonrenal component, Hande et al. [21] have shown that approximately 20%–40% is metabolic

Table 3. Examples of clinical conditions where etoposide elimination, metabolism, and (or) protein binding are affected: etoposide pharmacologic effect[a]

Excretion (renal)	Metabolism (hepatic)	Fraction of etoposide not bound to protein (f_u)	Anticipated pharmacologic effect
Normal	Normal	Increased (e.g., hypoalbuminemia)	None
Decreased	Normal	Normal	Increased
Normal	Decreased	Normal	Increased
Decreased	Normal	Increased (e.g., hypoalbuminemia)	Increased
Normal	Decreased	Increased (e.g., hypoalbuminemia)	None (?)
Decreased	Decreased	Increased	Increased

[a] Elimination and metabolism are assumed to remove etoposide from the body, and no active metabolite is formed via metabolism. The pharmacologic effect is directed against both normal tissue (toxicity) and tumor tissue (efficacy)

(primarily etoposide glucuronide formed in the liver and excreted in the urine). In a murine hepatotoxin model of liver disease, Hande and colleagues [20] found that impaired liver function decreased etoposide metabolic clearance. Impairment of hepatic function or alterations in plasma protein binding could also alter the disposition and pharmacologic effect of etoposide.

In the aforementioned study by D'Incalci et al. [12], 15 patients with hepatic dysfunction were studied [total bilirubin range, 0.5–32 mg/dl; gamma-glutamyl transpeptidase (γ-GT) range, 96–620 IU/l]. In all, 12 of these patients had pharmacokinetic parameters similar to those of the control group; however, the V_d and clearance values were much higher for 3 patients. No apparent difference was noted between these patients and the other patients with hepatic dysfunction. Serum albumin data were not presented, making it difficult to interpret completely the results of this study. The authors did not provide toxicity or tumor-response data, nor did they give dosing recommendations for patients with varying degrees of liver dysfunction.

In the population of patients studied by Arbuck and colleagues [1], total bilirubin values ranged from 0.2 to 23 mg/dl and serum albumin levels ranged from 2.2 to 4.0 g/dl. Systemic clearance of total etoposide, Vd_{ss} and half-life were not different in nine patients with total bilirubin levels of ≤ 1.0 mg/dl as compared with eight patients with abnormal bilirubin values (total bilirubin, > 1.0 mg/dl); however, the potential significance of changes in unbound etoposide clearance were not appreciated in this study. Toxicity and tumor-response data were not presented, and the authors could not provide quantitative dosing recommendations due to the small numbers of patients studied.

Hande and colleagues [21] studied the pharmacokinetics of etoposide in 11 patients with obstructive jaundice (total bilirubin, 2.0–16.0 mg/dl) and 23 patients with normal renal and hepatic function. Three patients with obstructive jaundice were restudied on a subsequent course of etoposide after the jaundice had resolved. No significant difference was noted in the pharmacokinetic parameters between the group with hyperbilirubinemia and the control group. The pharmacokinetic parameters in the three patients studied before and after recovery from jaundice were similar. Renal clearance was measured in 8 of the 11 patients with hyperbilirubinemia and 17 of the 23 controls, and no significant difference was observed (11.5 ± 3.2 vs 10.4 ± 3.9 ml min^{-1} m^{-2}). Metabolic clearance, primarily measured by the excretion of etoposide glucuronide in urine, was 4.9 ± 3.8 ml min^{-1} m^{-2} in patients with hyperbilirubinemia and 9.5 ± 6.9 ml min^{-1} m^{-2} in controls ($P = 0.13$). No measure of drug toxicity was provided by the authors, who opted instead to use measures of kinetic parameters to determine the effect of organ dysfunction on etoposide dosing.

Hande and colleagues [21] did address one of the most significant problems facing studies of this type, namely, having adequate statistical power to detect small differences between patients with hyperbilirubinemia and controls. In an "informal manner" Hande and colleagues pooled their data with those from D'Incalci et al. [12] and Arbuck and colleagues [1]. The combined data show that total etoposide clearance and half-life are not significantly altered in patients with hyperbilirubinemia (total bilirubin, 2–32 mg/dl) as compared with controls (power, 0.85 and 0.64, respectively).

This seeming contradiction involving a lack of change in etoposide systemic clearance in patients with abnormal total bilirubin levels (because of liver disease and a resulting decrease in intrinsic free clearance) could be explained by concomitant increases in unbound drug (e.g., bilirubin displacement and hypoalbuminemia), which offset the reduction of intrinsic free clearance in such patients [44]. Etoposide systemic clearance (e.g., 20 ml min^{-1} m^{-2}) is much lower than the liver blood flow (~ 800 ml min^{-1} m^{-2}) and thus, etoposide has a very low hepatic extraction ratio (ER, < 0.25). Using a model of hepatic elimination termed the venous equilibrium model, the hepatic clearance of a drug can be estimated by the following equation [6]:

$$CL_{hepatic} = Q\,[(f_p * Cl_{int})/(Q + f_p Cl_{int})].$$

In the case of etoposide, where Q is much greater than $f_p Cl_{int}$, then

$$CL_{hepatic} = f_p Cl_{int}.$$

The extent of plasma protein binding may be a primary determinant of hepatic clearance of poorly extracted drugs [4]. The terms binding-sensitive and binding-insensitive are used to describe the role of protein binding in this relationship. Drugs that are binding-insensitive have a fraction unbound of $> 15\%$ and their hepatic clearance is not "sensitive" to changes in plasma protein binding, whereas drugs that are binding-sensitive have a fraction unbound of $< 15\%$ and their hepatic clearance is "sensitive" to changes

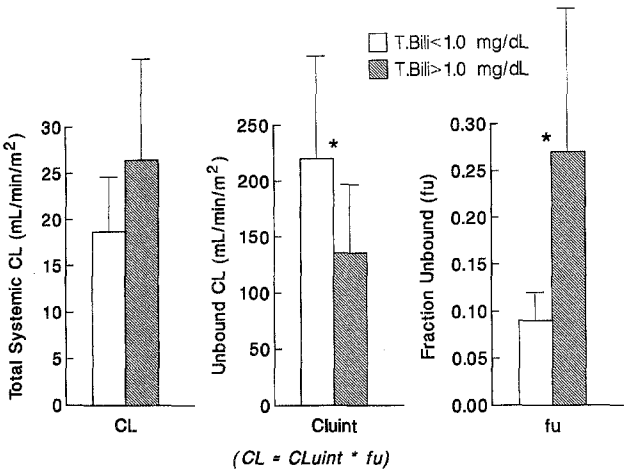

Fig. 4A–C. Bar graphs relating changes in **A** etoposide total systemic clearance, **B** unbound clearance, and **C** f_u for patients with total bilirubin values of <1.0 mg/dl (*open bars*) and patients with total bilirubin levels of >1.1 mg/dl (*hatched bars*). Statistically significant (*t*-test, $P<0.05$) differences between means are noted with an *asterisk* (from Stewart et al. [44])

in plasma protein binding. Using this terminology, etoposide could be classified as capacity-limited, binding-sensitive. Interpretation of etoposide plasma protein binding will provide additional information to improve our understanding of the disposition and use of etoposide in patients with liver dysfunction.

Initial reports of etoposide protein binding in patients with cancer and in plasma from normal volunteers showed an average fraction unbound of $13.9\% \pm 0.9\%$ and $4.3\% \pm 0.4\%$, respectively [43]. The etoposide binding ratio (binding ratio = $(1/f_u)$-1) was directly related to serum albumin levels ($r^2 = 0.83$, $p < 0.05$). In the cancer patients, the etoposide fraction unbound was correlated with total bilirubin and serum albumin levels. In a subsequent study, this model of total bilirubin and serum albumin was shown to be precise but biased toward overpredicting the etoposide fraction unbound [45]. However, in patients with hyperbilirubinemia (total bilirubin, >1.5 mg/dl) or hypoalbuminemia (serum albumin, <3.3 g/dl) the model was both precise and unbiased.

The role of protein binding in the disposition of etoposide was evaluated in 21 cancer patients receiving etoposide and cisplatin with a wide range of renal (creatinine clearance, 32.4–158.8 ml min^{-1} 1.73 m^{-2}) and hepatic function [total bilirubin, 0.3–21.5 mg/dl; aspartate aminotransferase (AST), 14–415 IU/l] [44]. As observed by other investigators, total etoposide systemic clearance was not significantly different between patients with total bilirubin levels of <1.0 mg/dl ($n = 15$) as compared with patients with total bilirubin values of >1.1 mg/dl (18.7 ± 5.9 vs 26.4 ± 10.7 ml min^{-1} m^{-2}, respectively). However, the mean etoposide fraction unbound was 0.09 ± 0.03 in the group with total bilirubin levels of <1.0 mg/dl as compared with 0.27 ± 0.15 in the group with elevated total bilirubin values. The unbound etoposide concentration was measured in each plasma sample, and the unbound clearance (clearance of unbound drug, f_pCl_{int}) was significantly lower in the patients with elevated levels of bilirubin (220 ± 90 vs 135 ± 61.1 ml min^{-1} m^{-2}; $p < 0.05$). The reduction in unbound clearance and increase in fraction unbound leading to offsetting changes in total clearance is depicted in Fig. 4.

Although this study provided an explanation for the lack of change in etoposide total clearance in patients with liver dysfunction, the important question that remained, was whether this was clinically significant. In a subsequent study, a relationship was noted between etoposide systemic exposure (AUC) and hematologic toxicity (percentage of decrease in white blood cells) [46]. As the exposure to etoposide increased, a greater decrease in the WBC was observed. Although this relationship was noted for both total and unbound etoposide, the parameters of the model using unbound etoposide were estimated more precisely.

In this study, measurement of unbound etoposide provided more information about dosing of etoposide than did a knowledge of the exposure to total etoposide. For example, the average total systemic exposure (AUC) for patients with total bilirubin levels of <1.0 mg/dl was 309 mg h l^{-1} as compared with 236 mg h l^{-1} for patients with total bilirubin values of >1.0 mg/dl (70% lower AUC), whereas the systemic exposure to unbound etoposide in the two groups was 27 and 36 mg h l^{-1}, respectively (25% higher AUC). On the basis of the results of the pharmacodynamics study, those patients with an elevated level of bilirubin will have an elevated systemic exposure to unbound (or active) drug and will have a greater effect (decrease in WBC). Whether adjusting the therapy on the basis of the exposure to unbound etoposide will improve the efficacy of etoposide remains to be studied prospectively.

Many investigators have found albumin to be important in the analysis of total etoposide pharmacokinetics [1, 34, 40, 41]. These investigators found that serum albumin explained a significant amount of the variability observed in etoposide pharmacokinetic parameters.

Morritu and colleagues [32] reported on the clinical and biochemical factors associated with early mortality in 71 of 610 patients with small-cell lung cancer. These patients were treated with a regimen including etoposide (100 mg t.d.s. given orally on days 1–3), cyclophosphamide (1 g/m^2 given i.v. on day 1), and vincristine (2 mg given i.v. on day 1). As a group, patients with higher alkaline phosphatase levels, elevated blood urea nitrogen (BUN) values, lower serum albumin levels, and palpable hepatomegaly were more likely to die within the first course of chemotherapy as compared with controls. This observation provides additional indirect evidence that alterations in protein binding may have clinical consequences.

Pharmacodynamics

Pharmacodynamics refers to the relationship between drug concentrations at the site of action (receptor) and pharmacologic response (toxicity and efficacy) [37]. Pharmacokinetic parameters provide quantitative information (e.g., clearance, systemic exposure) about the disposition of a drug in the body but reveal nothing about what effect the drug may have. Creation of pharmacodynamic models in-

tegrates information about drug disposition (pharmacokinetics) and drug effect to provide the oncologist with a model to determine the drug dose needed to optimize therapy (minimize toxicity and maximize efficacy).

Relatively few studies of the pharmacodynamics of etoposide have been published [30, 31, 36, 46]. Even fewer studies have been performed in patients with impaired renal and (or) hepatic function. Most of the published studies have reported the relationship between exposure to total (bound and unbound) etoposide and myelotoxicity. The significance of systemic exposure to unbound etoposide with regard to the pharmacologic effect (efficacy and toxicity) is not well defined. Results of initial studies of unbound etoposide systemic exposure suggest that alterations in protein binding may be clinically relevant, at least to myelotoxicity [46]. Indirectly, the importance of protein binding to etoposide pharmacodynamics has been suggested by Ratain et al. [30, 36]. The optimal model to explain the observed interpatient variability in myelosuppression contained albumin as a variable [30, 36].

As stated above, pharmacodynamic relationships established in patients with normal renal and hepatic function cannot be extrapolated to patients with organ dysfunction. The potential effects of the renal and hepatic disease as well as the other drugs used in these patients on the pharmacodynamic target must be considered. Thus, studies of etoposide pharmacokinetics and pharmacodynamics should be performed in populations of patients with renal and hepatic dysfunction that are large enough for the establishment of dosing guidelines. Until the results of these studies are available, clinicians are left to use the currently available information to establish dosing recommendations.

Recommendations

Changes in etoposide pharmacokinetics alone should not form the basis for dose modifications, although they can aid in our understanding of the altered drug toxicity and (or) therapeutic efficacy associated with impairment of renal and (or) hepatic function. Quantitation of the relationship between pharmacokinetics and clinical outcome (pharmacodynamics) will provide the clinician with a model to optimize the etoposide dose for an individual patient.

As discussed in this paper, three primary determinants of etoposide disposition and, presumably, pharmacologic effect include elimination (renal), metabolism (hepatic), and protein binding. In a clinical situation where one or more of these determinants is affected, the potential exists for etoposide's pharmacologic effect to be affected as well. Table 3 provides several examples of clinical conditions of altered elimination, metabolism, and (or) protein binding and the anticipated pharmacologic effect.

Investigators have empirically recommended specific etoposide dose decreases for various ranges of organ function; however, in the absence of prospectively validated dosing recommendations, any recommendations for dose alterations can be considered only as guidelines for initial dosing. Subsequent etoposide doses should be based on clinical effects and the tolerance of the patient. The extent to which the etoposide dose is reduced must be determined by the clinician on the basis of not only the organ function but also the current condition of the patient (e.g., Karnofsky or Eastern Cooperative Oncology Group performance status), previous cytotoxic chemotherapy, and the therapeutic goal (palliation versus cure). Arbitrary reductions in the etoposide dose based solely on estimates of renal and hepatic function without regard to pharmacologic effect may lead to overdosing and toxicity or to underdosing and inadequate antitumor effects.

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