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Carboplatin and etoposide pharmacokinetics in patients with testicular teratoma

David R. Newell[1], Rosalind A. Eeles[2], Lindsey A. Gumbrell[1], Francis E. Boxall[1], Alan Horwich[2], and A. Hilary Calvert[1]

[1] Drug Development Section, Institute of Cancer Research and [2] Section of Radiotherapy, Royal Marsden Hospital, Sutton, Surrey, UK

Summary. The pharmacokinetics of carboplatin and etoposide were studied in four testicular teratoma patients receiving four courses each of combination chemotherapy consisting of etoposide (120 mg/m^2 daily × 3), bleomycin (30 mg weekly) and carboplatin. The carboplatin dose was calculated so as to achieve a constant area under the plasma concentration vs time curve (AUC) of 4.5 mg carboplatin/ml × min by using the formula: dose = $4.5 \times (GFR + 25)$, where GFR is the absolute glomerular filtration rate measured by ^{51}Cr-EDTA clearance. Carboplatin was given on either day 1 or day 2 of each course and pharmacokinetic studies were carried out in each patient on two courses. Etoposide pharmacokinetics were also studied on two separate courses in each patient on the day on which carboplatin was given and on a day when etoposide was given alone. The pharmacokinetics of carboplatin were the same on both the first and second courses, on which studies were carried out with overall mean ±SD values (n = 8) of 4.8±0.6 mg/ml × min, 94±21 min, 129±21 min, 20.1±5.41, 155±33 ml/min and 102±24 ml/min for the AUC, beta-phase half-life ($t_{1/2\beta}$), mean residence time (MRT), volume of distribution (Vd) and total body (TCLR) and renal clearances (RCLR), respectively. The renal clearance of carboplatin was not significantly different from the GFR (132±32 ml/min). Etoposide pharmacokinetics were also the same on the two courses studied, with overall mean values ±SD (n = 8) of: AUC = 5.1±0.9 mg/ml × min, $t_{1/2\alpha}$ = 40±9 min, $t_{1/2\beta}$ = 257±21 min, MRT = 292±25 min, Vd = 13.3±1.31, TCLR = 46±9 ml/min and RCLR = 17.6±6.3 ml/min when the drug was given alone and AUC = 5.3±0.6 mg/ml × min, $t_{1/2\alpha}$ = 34±6 min, $t_{1/2\beta}$ = 242±25 min, MRT = 292±25 min, Vd = 12.5±1.81, TCLR = 43±6 ml/min and RCLR = 13.4±3.5 ml/min when it was given in combination with carboplatin. Thus, the equation used to determine the carboplatin accurately predicted the AUC observed and the pharmacokinetics of etoposide were not altered by concurrent carboplatin administration. The therapeutic efficacy and toxicity of the carboplatin-etoposide-bleomycin combination will be compared to those of cisplatin, etoposide and bleomycin in a randomised trial.

Offprint requests to: David R. Newell, Clinical Pharmacology, Block E, Institute of Cancer Research, Cotswold Road, Belmont, Sutton, Surrey, UK, SM2 5NG

Introduction

The treatment of testicular teratoma is one of the success stories of cancer chemotherapy. Using cisplatin-based combination chemotherapy, over 90% of good-prognosis patients and the majority of poor-prognosis patients can be expected to achieve a complete remission, with a high probability of being disease-free at 5 years (recent results were reviewed by Ozols and Yagoda [19]). Current clinical objectives in the management of this disease fall into two major areas, namely, the improvement of response rates in poor-prognosis patients and the reduction of the toxicity of therapy given to favorable-prognosis individuals [19]. With regard to the latter objective, of the agents used as standard therapy (cisplatin, bleomycin and vinblastine or etoposide), cisplatin is the most toxic compound. Its acute toxicity consists primarily of nausea and vomiting; however, of greater concern are the chronic side effects of nephrotoxicity, neurotoxicity and ototoxicity. Thus, in a study of the toxic effects of cisplatin, vinblastine and bleomycin combination chemotherapy (PVB), Vogelzang and coworkers [28] recorded a mean decline in creatinine clearance from 115 to 65 ml/min after six courses. Other workers have observed persistent neurotoxicity as indicated by alterations in sensory perception, particularly to touch and vibration [25].

Recognition of the problems associated with cisplatin-based therapy led a number of drug development groups to search for a less toxic platinum complex [12]. This search resulted in the clinical evaluation of a series of complexes, of which carboplatin remains the lead compound. In a large number of phase I and II studies carboplatin has shown no clinically significant nephrotoxicity, neurotoxicity or ototoxicity despite its being given without hydration or diuresis [2, 9, 27]. In addition, carboplatin is less emetogenic than cisplatin and in studies thus far reported, the former has displayed antitumour activity similar to that of the latter. Thus, carboplatin appears to represent a major advance towards the goal of less toxic cancer chemotherapy.

In view of these results, a pilot study of the activity of carboplatin in the treatment of testicular tumours was carried out [20]. This study demonstrated that carboplatin was indeed active as a single agent for the treatment of seminoma patients and for the treatment of teratoma patients as well when given in combination with etoposide and bleomycin. The toxicity of both treatments was mild. Howev-

er, at this time it became clear that dosing with carboplatin on the basis of surface area might not be the optimal method. Studies by Harland et al. [11] and Egorin et al. [7] have demonstrated that renal excretion is the major route of carboplatin elimination and that glomerular filtration is the operating mechanism. Thus, in patients with impaired renal function, dosage on the basis of surface area can lead to untoward toxicity [2, 7]. Conversely, in patients with above average renal function, dosing on the basis of surface area might lead to inadequate drug exposure. Since GFR values of > 120 ml/min are not uncommon in young males with testicular cancer, it was felt that compensation for interpatient variation in GFR was essential in any prospective study of the role of carboplatin in the therapy of this disease.

We have recently reported a simple formula for the calculation of the dose of carboplatin required to achieve a predetermined free plasma carboplatin AUC: dose = AUC × (GFR + 25) [3]. In this equation the GFR is absolute, not being normalised to a given surface area, and the constant 25 represents non-renal clearance. Since reaction with tissues is thought to be the major route of non-renal clearance and total tissue mass is a function of surface area, this term represents a mean value. However, for the majority of adults body surface area falls within the range of 1.5–2.0 m^2; for practical purposes the non-renal clearance can thus be considered to be constant.

The present paper describes a pilot study of the use of the above formula to determine the carboplatin dose for patients treated with the carboplatin-etoposide-bleomycin combination. The aim of the study was to measure the carboplatin AUC achieved in patients on two separate courses. The target carboplatin AUC (4.5 mg/ml × min) was chosen on the basis of the predicted AUC values and observed toxicities in our earlier study [20]. In addition, the pharmacokinetics of etoposide were investigated, since it has been suggested that prior cisplatin therapy can lead to an alteration in etoposide disposition [21, 24]. To achieve this, etoposide levels were measured on two separate courses of therapy on the day on which carboplatin was given and on a day on which etoposide was given alone.

Materials and methods

Patients. Four patients with previously untreated testicular teratoma were studied; their characteristics are given in Table 1. Etoposide was injected as a 30-min i.v. infusion dissolved in 250 ml isotonic saline at a dose of 120 mg/m^2 per day on days 1–3 of a 3-week cycle. Carboplatin was given as a 60-min i.v. infusion in 500 ml 5% dextrose on either day 1 or day 2 of each cycle. The carboplatin was given after the etoposide via the same i.v. line after the latter had been flushed with 100 ml isotonic saline for 15 min. The carboplatin dose was calculated by the formula

Dose (mg) = 4.5 × (GFR + 25).

The GFR was measured by ^{51}Cr-EDTA clearance [4] and was the absolute value (ml/min), with no correction for surface area. Bleomycin was given as an i.v. bolus at a dose of 30 mg weekly. Patients received a total of four courses of therapy and gave their informed consent in accordance with the guidelines of the Royal Marsden Hospital Ethical Committee.

Sample collection. Blood samples (5 ml) were collected from an indwelling i.v. cannula placed in the arm opposite to that receiving the drugs. Samples were taken into heparinised tubes (10 IU/ml) prior to the start of drug administration, mid-infusion, at the end of the infusion and 0.25, 0.5, 1, 1.5, 2, 4, 6, 9, 12, 18 and 24 h after the end of the infusion. Plasma and plasma ultrafiltrates for carboplatin analyses were prepared immediately as previously described [11, 17]. For etoposide analyses plasma was prepared immediately as described above and stored frozen (−20° C). Pooled 0- to 24-h urine samples were collected at room temperature, the total volume was recorded and an aliquot stored frozen (−20° C).

Drug analyses. Plasma carboplatin levels were measured by flameless atomic absorption spectrophotometric analysis of the platinum in the plasma ultrafiltrate as previously described [11, 17], since it has been shown that ultrafiltrable platinum following carboplatin exists solely in the form of intact carboplatin and that there is no significant reversible binding of carboplatin to plasma macromolecules [8, 11]. All results are expressed as μg or mg carboplatin/ml, not elemental platinum.

Plasma etoposide levels were determined by HPLC with UV detection using previously published methods with minor modifications [6]. Etoposide was extracted from 0.5-ml aliquots of plasma by rotary mixing with 2.5 ml chloroform for 1 min in 15-ml glass centrifuge tubes. The layers were clarified by centrifugation for 15 min at 1,000 *g* at room temperature, and the entire organic layer was removed and concentrated to dryness in a stream of nitrogen at 40° C. The concentrated sample was reconstituted in 0.2 ml HPLC mobile phase and 0.15 ml was analysed by HPLC. Separations were carried out on a Waters Associates chromatograph (Millipore, UK; Harrow, UK) fitted with a 15 × 0.21-cm Spherisorb phenyl column (Phase Sep; Queensferry, Clwyd, UK) and a 5 × 0.21-cm CO:Pell ODS precolumn (Whatman; Clifton, NJ, USA). Etoposide was eluted isocratically with water:methanol 6:4 (v/v) at a flow rate of 1 ml/min and detected by UV absorbance at 254 nm. Peak identification was done by co-chromatography with authentic etoposide and by UV absorbance ratio analysis at 254 nm and again at 280 nm in comparison with authentic etoposide. Quantitation was carried out by external standardisation, since preliminary experiments showed that this gave greater accuracy than that obtained using teniposide as an internal standard. The above assay was linear over the range of 0.2–30 μg/ml (r = 0.999), with intra- and inter-assay coefficients of variation of 5% and 10%, respectively. The analytical samples of etoposide and teniposide used in these studies were a gift from Bristol laboratories (East Syracuse, NY, USA).

Pharmacokinetic analyses. Plasma concentration vs time data were analysed by non-linear least-squares regression [14] using the weighting function $1/(Y + \hat{Y})^2$ [18]. Following the end of the infusion, a mono-exponential equation was fitted to the carboplatin concentration vs time data:

$C = Ae^{-\alpha t}$,

where C is the concentration at time t and A and α are the concentration and first-order rate constants, respectively. A was corrected for the period of the infusion [16] and the following pharmacokinetic parameters were calculated using standard equations [13]:

Table 1. Characteristics of patients treated with carboplatin, etoposide and bleomycin chemotherapy

Patient	Disease (stage)[a]	GFR (ml/min)	Surface area (m^2)	Carboplatin dose (mg)	Pharmacokinetics (courses studied)
1	MTI 2B	177	1.9	900	1,3
2	MTU 2A	131	1.9	700	1,2
3	MTU 2B	115	1.8	650	1,2
4	MTT 4CLI	113	1.9	600	3,4

[a] Disease stage as defined by Peckham et al. [20]

AUC = A/α;
Half-life = $0.693/\alpha$;
Mean residence time (MRT) = $(A/\alpha^2)/AUC$;
Volume of distribution (Vd) = Dose × $(A/\alpha^2)(AUC^2)$;
Total body clearance (TCLR) = Dose/AUC; and
Renal clearance (RCLR) = Amount excreted in urine/AUC.

Following the end of the etoposide infusion, a bi-exponential equation was fitted to the data:
$C = Ae^{-\alpha t} + Be^{-\beta t}$,
where C is the concentration at time t and A, B and α, β are the concentration and first-order rate constants, respectively. Following correction for the infusion period [16], pharmacokinetic parameters were again calculated using standard formulae [13] as follows:
AUC = $A/\alpha + B/\beta$;
Half-lives = $0.693/\alpha$ or β;
MRT = $((A/\alpha^2) + (B/\beta^2))/AUC$;
Vd = Dose × $((A/\alpha^2)+(B/\beta^2))/(AUC^2)$;
TCLR = Dose/AUC; and
RCLR = Amount excreted in urine/AUC.

Statistical differences between sets of data were investigated using Student's t-test, with the paired test being applied where comparisons involved data from the same patient on two different courses. Where no significant difference was found, P value for the t value obtained was >0.1.

Plasma protein binding of etoposide. In an attempt to measure the free etoposide levels in plasma, 25-µl aliquots of plasma ultrafiltrates, prepared as previously described [11, 17], were analysed by HPLC as given above. The recovery of etoposide from the ultrafiltration membranes was determined using etoposide dissolved in either water or control heparinised human plasma at 10, 20, 50 and 100 µg/ml. Over this concentration range, etoposide recovery from water was complete (98% ± 5%). Recovery from human plasma was concentration-dependent, i.e. 3%, 4%, 9%, and 25% at 10, 20, 50 and 100 µg/ml, respectively.

Results

Carboplatin pharmacokinetics

The plasma levels of carboplatin following its administration as a 60-min i.v. infusion are shown in Fig. 1. As can be seen, levels declined mono-exponentially following the end of the infusion. The plasma levels of carboplatin were the same in all four patients on both of the courses on which they were studied; the pooled pharmacokinetic parameters for all eight courses are given in Table 2. Particularly important is the observation that the AUC value was 4.8 ± 0.6 mg/ml × min (mean ± SD; n = 8). Since the carboplatin dose was intended to achieve an AUC of

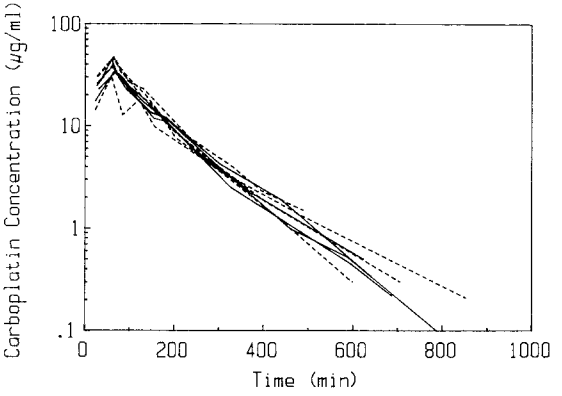

Fig. 1. Plasma carboplatin concentrations in four patients treated with a 60-min i.v. infusion of carboplatin on two occasions. *Solid lines* represent the first course studied and *broken lines*, the second course. For the courses studied see Table 1

4.5 mg/ml × min, this indicates that the dosage formula used accurately predicts the AUC achieved. The mean renal clearance of carboplatin as well as its urinary excretion are also given in Table 2. Table 1 slows that the mean GFR value for these patients (132 ± 32 ml/min) was not significantly different from the mean carboplatin renal clearance (102 ± 24 ml/min).

Etoposide pharmacokinetics

The pharmacokinetics of etoposide were studied following the administration of the drug alone as well as after its administration in combination with carboplatin. Figure 2 shows the plasma levels of etoposide given in combination with carboplatin; again, there were no differences in the pharmacokinetics when the first and second studies in each patient are compared. Similarly, as shown in Fig. 3, there were no differences in the pharmacokinetics of etoposide on the two courses studied in each patient when it was given alone. The two sets of pharmacokinetic parameters, for either etoposide in combination with carboplatin or etoposide alone, are given in Table 2. These data clearly show that the co-administration of carboplatin did not alter etoposide pharmacokinetics. The urinary excretion and renal clearance of etoposide given alone or in combination with carboplatin are also shown in Table 2. Once again, the co-administration of carboplatin did not alter the renal elimination of etoposide. Attempts to measure the levels of free etoposide in the ultrafiltrates of plasma samples from patients receiving etoposide either alone or in combination with carboplatin proved unsuccessful. Since the binding of etoposide to control human plasma was found to be >95% at 10 and 20 µg/ml (see *Materials and methods*), the levels

Table 2. Pharmacokinetic parameters for carboplatin and etoposide in patients treated with carboplatin, etoposide and bleomycin chemotherapy

Compound	Carboplatin	Etoposide	
Therapy	Carboplatin + etoposide	Etoposide alone	Carboplatin + etoposide
AUC (mg/ml × min)	4.8± 0.6	5.1± 0.9	5.3± 0.6
$t_{1/2\alpha}$ (min)	ND	40 ± 9	24 ± 6
$t_{1/2\beta}$ (min)	94 ±21	257 ±21	242 ±23
MRT (min)	129 ±21	292 ±35	292 ±25
Vd (l)	20.1± 5.4	13.3± 1.3	12.5± 1.8
Total plasma clearance (ml/min)	155 ±33	46 ± 9	43 ± 6
Renal clearance (ml/min)	102 ±24	17.6± 6.3	13.4± 3.5
Urinary excretion (0–24 h, % of dose)	68 ±14	39 ±13	31 ± 9

Values represent the mean ± SD of eight determinations for each parameter; ND, not detected

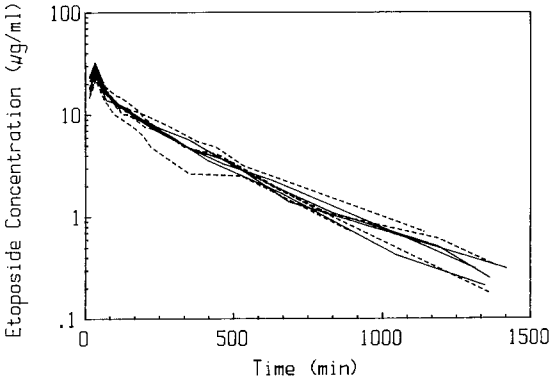

Fig. 2. Plasma etoposide concentrations in four patients treated with a 30-min i.v. infusion of etoposide (120 mg/m^2) in combination with carboplatin on two occasions. *Solid lines* represent the first course studied and *broken lines*, the second course. For the courses studied see Table 1

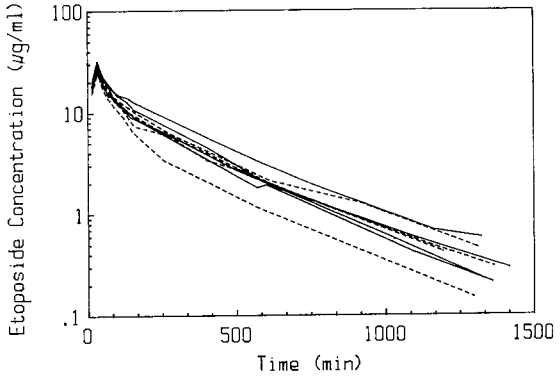

Fig. 3. Plasma etoposide concentrations in four patients treated with a 30-min i.v. infusion of etoposide (120 mg/m^2) on two occasions. *Solid lines* represent the first course studied and *broken lines*, the second course. For the courses studied see Table 1

expected for even the peak plasma etoposide concentration would be at or near the limit of detection of the assay used (0.2 μg/ml). Thus, the effect of carboplatin administration on free etoposide levels could not be determined.

Discussion

The aim of the present study was to validate the use of a simple formula to calculate the carboplatin dose required for combination therapy with etoposide and bleomycin for the treatment of testicular teratoma and to investigate the effect of carboplatin co-administration on etoposide pharmacokinetics. The impetus to study the use of such a formula, in which the dose is determined primarily be renal function, stems from studies on the pharmacokinetics of carboplatin [7, 11]. Thus, as in the present study (Table 2), renal excretion is the major route of drug elimination in patients with normal renal function, with the mechanism being glomerular filtration. Since renal function can vary independently of surface area as a result of, for example, age, disease state and prior nephrotoxic chemotherapy, it is important to compensate for the renal function status of a patient in determining the dose of a drug that undergoes significant renal elimination. For the field of cancer chemotherapy this area has been reviewed by Powis [22].

Previous studies on the combination of carboplatin, etoposide and bleomycin used a dose of 300 mg/m^2 carboplatin [20] and on the basis of the dosage formula we have recently described [3], it can be calculated that a 1.7-m^2 patient with a GFR of 100–120 ml/min will receive a carboplatin exposure (AUC) of 3.5–4 mg/ml × min following this dose. Since the toxicity associated with this exposure was minimal, 4.5 mg/ml × min was chosen as the target AUC in the present study. As shown in Table 2, the target AUC was accurately achieved despite one patient's having a GFR of 177 ml/min; Table 1 shows that the doses given to the patients were in fact equivalent to 320–470 mg/m^2. Hence, calculation of the dose using this formula gave rise to a more reproducible carboplatin exposure (AUC) than would have been expected had a fixed dose per square meter been used.

Overall, the pharmacokinetic parameters determined for carboplatin in this group of patients (Table 2) are in close agreement with those previously reported [5, 7, 8, 11, 15, 17, 23, 26], which cover a range of doses and include data for carboplatin given alone [5, 7, 11, 15, 23, 26] as well as for carboplatin given together with etoposide [23; present study] and in combination with doxorubicin [8]. Thus, the current consensus in the literature is that carboplatin is a drug that displays linear pharmacokinetics and does not suffer drug interaction problems with other cytotoxic agents. The only significant determinant of carboplatin pharmacokinetics appears to be renal function, and this is a factor that can readily be compensated for by the use of a simple formula.

The second objective of this study was to examine the effect of the co-administration of carboplatin on the pharmacokinetics of etoposide; the latter have been the subject of a large number of studies that were recently reviewed in detail by Pfluger and colleagues [21]. In two separate studies it has been shown that the clearance of etoposide is reduced in patients who have had prior cisplatin therapy [21, 24], although other authors have failed to demonstrate this effect [1, 10]. D'Incalci et al. [6] have recently clearly

defined the mechanism that probably underlies the observation that etoposide clearance can be reduced in patients with previous exposure to cisplatin. These authors studied etoposide clearance in 26 patients with creatinine clearances ranging from 4 to 100 ml/min per m^2 and demonstrated a highly significant positive relationship. Thus, it seems most probable that for those patients who have previously received cisplatin and subsequently show reduced etoposide clearance, the mechanism operating is simply reduced urinary excretion as a consequence of the impaired renal function induced by cisplatin. This explanation is in accord with the results reported by D'Incalci et al. [6], who observed reduced urinary excretion of etoposide in patients with impaired renal function as compared with that observed in patients with normal kidney function.

In the light of the above discussion, it is perhaps not surprising that the co-administration of carboplatin did not alter the pharmacokinetics of etoposide (Table 2) or that the pharmacokinetics of etoposide were the same on both the first and second courses studied (Figs. 2 and 3). Carboplatin produces neither acute nor chronic nephrotoxicity; thus, an alteration in pharmacokinetics following cisplatin via the suggested mechanism would not be expected.

In addition to gross changes in the pharmacokinetics of etoposide, the possibility of carboplatin-induced changes in the plasma protein binding of etoposide was considered. Carboplatin is known to undergo irreversible binding to plasma proteins [5, 11, 26]; hence, the ability of the proteins to bind etoposide could be impaired. However, at the concentrations encountered (<30 μg/ml), the levels of free etoposide were too low to be measured accurately; hence, the effect, if any, of carboplatin on etoposide protein binding could not be determined. This level of etoposide protein binding ($>95\%$) is in agreement with that previously reported by Gouyette et al. [10].

In conclusion, the present study shows that the dose of carboplatin required to achieve a given AUC can readily be determined by a simple formula that compensates for variations in renal function between patients. Furthermore, this study shows that there is no apparent pharmacokinetic interaction between carboplatin and etoposide. Using the carboplatin dosage formula validated in this study, with a target AUC of 5 mg/ml × min, the comparative toxicity and efficacy of cisplatin, etoposide and bleomycin vs carboplatin, etoposide and bleomycin will be evaluated in a randomised trial. It is hoped that this study will represent a further step towards low-toxicity curative therapy in testicular cancer.

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