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Pharmacokinetics of unchanged carboplatin (CBDCA) in patients with small cell lung carcinoma

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Summary. The disposition of the cisplatin analogue carboplatin was studied in seven patients with small cell lung cancer. Carboplatin 100 mg/m^2 was administered without hydration by a 1-h infusion with VP16-213 120 mg/m^2 on days 1, 2 and 3 of each course. Plasma and urine collections were made on days 1 and 3 of the first course of treatment. Carboplatin levels in plasma ultrafiltrate and urine were quantitated using a specific and sensitive, high-performance liquid chromatographic assay which involved sample clean-up on a Dowex-2 column prior to injection. Estimates of pharmacokinetic parameters determined using either compartmental or non-compartmental methods were comparable. There was no difference between carboplatin pharmacokinetic parameters determined on days 1 and 3 of treatment. The mean (± SD) carboplatin half-life determined from plasma data on day 1 was 105 ± 30.4 min and was not significantly different from that determined using urinary excretion rate data (107 ± 51.7 min). Urinary excretion rate plots showed that carboplatin elimination was mono-exponential for up to 14 h after infusion. Total-body clearance was 105 ± 40.0 ml min^{-1} m^{-2}, renal clearance 64.3 ± 44.1 ml min^{-1} m^{-2}, and volume of distribution 17.3 ± 4.2 l/m^2 on the 1st day of treatment. Of the administered dose, $58.4\% \pm 21.2\%$ was recovered in urine over a 24-h period after the start of the infusion. The mean renal clearance of carboplatin was comparable to creatinine clearance. Carboplatin disposition was clearly defined in the patients studied using analytical methodology specific for the unchanged drug.

Introduction

Carboplatin (CBDCA, diamminecyclobutanedicarboxylatoplatinum) is a cisplatin analogue with activity against a number of human tumours [1–3, 5, 8, 11, 12, 17]. Unlike cisplatin, it has shown little evidence of significant nephrotoxicity at the dose levels reported in phase II trials in patients. Carboplatin also appears less emetogenic, neurotoxic and ototoxic than cisplatin, with myelosuppression, particularly thrombocytopenia, becoming dose-limiting [1, 2, 5, 8, 11, 17, 18].

Carboplatin disposition in patients differs markedly from that of cisplatin in a number of respects. Irreversible protein binding occurs only slowly in comparison with cisplatin. The majority of total platinum in plasma after i.v. administration of carboplatin consists of unchanged drug [8]. There has also been no evidence of active secretion of carboplatin in the kidney [1, 3, 4, 8], whereas cisplatin clearly undergoes active secretion and reabsorption [9, 14]. The half-life of unchanged carboplatin in patients is approximately 90 min, compared with 30 min for cisplatin. Different chemical reactivity and lipophilicity can be postulated as the basis for the marked differences in disposition between the two drugs.

Several studies of ultrafilterable platinum disposition after carboplatin administration to patients have been reported [1–4, 8, 11, 18]. However, there has been only one report of the pharmacokinetics of unchanged drug in patients [8]. Carboplatin was administered as a single 1-h infusion at a dose of 300–500 mg/m^2 and levels measured by high – performance liquid chromatography. We have modified this method by the introduction of a clean-up step prior to chromatography. This has extended the detection limits to 0.5 µg/ml for carboplatin in plasma ultrafiltrate. The method was applied to a pharmacokinetic study in patients with small cell lung cancer who received carboplatin 100 mg/m^2 with VP16-213 120 mg/m^2 on days 1, 2 and 3 by 1-h infusion. Plasma ultrafiltrate and urinary levels of carboplatin were quantitated and the disposition of the drug compared on days 1 and 3. The enhanced sensitivity of the assay allowed complete definition of carboplatin pharmacokinetics at the 100 mg/m^2 dose level.

Materials and methods

Patients. All patients had histologically or cytologically proven small cell lung cancer. No patient had received prior chemotherapy or radiotherapy. Eligible patients were required to have pretreatment neutrophil counts >1500/ul, platelet counts >100000/µl, and serum creatinine <0.15 mmol/l and/or creatinine clearance of >40 ml/min. All patients gave informed consent before proceeding with the study. VP16-213 120 mg/m^2 was given i.v. daily on days 1, 2 and 3 in 500 ml normal saline over 1 h. Blood pressure recordings were performed before treatment, after 30 min, and at the end of the infusion. Carboplatin 100 mg/m^2 was also given i.v. daily on days 1, 2 and 3 in 500 ml normal saline over 1 h. No pre- or post-hydration was given. Seven patients were studied on days 1 and 3 of the first course of treatment.

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Sample collection. Blood samples (5–6 ml) were collected into polypropylene tubes containing EDTA immediately before the administration of carboplatin and 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 12 and 24 h after the start of the infusion. Samples were taken through a Teflon catheter and heparin lock from an arm vein. Samples were grouped and kept on ice for up to 1 h and were then immediately centrifuged at 4 °C. Plasma was then immediately frozen and stored at −70 °C until all collections were complete. Plasma was stored at −70 °C for up to 48 h and was then thawed and ultrafiltered through 25000 mol. wt. cut-off cones (CF-25A Centriflo from Amicon, Lexington, Mass, USA) at 4 °C. Studies by Gaver and Deeb [6] have shown that the in vitro half-life of carboplatin in plasma (6 µg/ml) at −25 °C was 49 days. The present storage conditions were therefore unlikely to result in any appreciable loss of the drug from plasma. The stability of carboplatin (10 µg/ml) determined in vitro in plasma containing EDTA was comparable ($t^{1/2}$ > 24 h at 37 °C) to that reported by Gaver and Deeb [6] (32 h), indicating that the anticoagulant did not reduce unchanged carboplatin stability. Plasma ultrafiltrate was stored in polystyrene tubes at −70 °C for up to 1 week prior to analysis. Urine was collected immediately before infusion and separately each time patients voided for the period up to 24 h after the start of the infusion. The volume was noted and a 10 ml aliquot stored in polypropylene tubes at −70 °C. All samples were transported in dry ice.

Assay methods. Plasma ultrafiltrate and urine were assayed specifically for carboplatin by high – performance liquid chromatography. Samples (0.5 ml) were first purified by passage through 1 ml water-washed Dowex-2 packed in a pasteur pipette. The Dowex was then washed with 2 × 0.5 ml water and all eluates combined, after which 10 µl of the eluates was injected directly into the chromatograph. Chromatography was carried out on a 250 × 4.6 mm, 5-µm silica column (Brownlee Assoc., Santa Clara, Calif, USA) using a mobile phase of 90% acetonitrile – 10% water as described by Harland et al. [8]. A silica saturation column was installed in the solvent line prior to the injection valve to improve column life. The mobile phase flow rate was 2 ml/min and the eluate was monitored at 225 nm. Detection limits of the assay were 0.5 and 5.0 ug/ml in plasma ultrafiltrate and urine, respectively. The intra-assay variation was less than 5% over the concentration range 0.5–10 µg/ml in plasma ultrafiltrate and 5–100 ug/ml in urine. VP16-213 did not interfere in the assay.

Pharmacokinetic analyses. Plasma ultrafiltrate levels of carboplatin were analysed by both compartmental and non-compartmental methods. The former involved the use of a one-compartment model where both intra- and post-infusion data were fitted simultaneously. This approach has been shown to provide more accurate estimates of equation parameters than the use of either intra- or postinfusion data separately [10]. The following equation: $C = C' * (1 - e^{K}T) * e^{-K}t$ was used to model the data, and final parameter estimates were obtained without weighting, using the BMDP nonlinear least-squares analysis program NONLINEAR. In this equation, K was the first-order rate constant for elimination, T the infusion time, t the time after the start of the infusion, C' a constant, and C the predicted concentrations of carboplatin in the plasma ultrafiltrate. Estimates of clearance, volume of distribution and half-life were determined from the coefficients, C' and K [7, 10].

The non-compartmental approach involved determination of the total area under the curve and area under the the first moment curve as described by Gibaldi and Perrier [7]. Clearance and volume of distribution were determined from these parameters. Terminal half-life was determined by regression analysis. Estimates of clearance, volume of distribution and half-life determined using compartmental and non-compartmental methods were compared.

Urinary excretion rates were determined for each urine collection period and plotted against the time after infusion. Such plots were possible for five patients on day 1 of treatment and six patients on day 3 of treatment. The plots were used to check estimates of the plasma carboplatin half-life and to confirm that carboplatin levels declined mono-exponentially. Carboplatin renal clearance was determined from the amount of carboplatin excreted over the 24-h duration of the study by the corresponding area under the curve for carboplatin in plasma ultrafiltrate for the same period, which, in general, corresponded to the total area under the curve. The percentage of the platinum dose excreted in urine was determined for the 24-h period of the study.

Creatinine clearance was determined using the 12-h plasma sample and the 24-h urine collection made at the time of the pharmacokinetic studies.

Statistical analyses. Comparisons between paired data were performed using Student's *t*-test (two tailed). A 0.05 level of significance was used in all comparisons.

Results

Carboplatin levels in plasma ultrafiltrate are shown in Fig. 1 for patient 4 on days 1 and 3 respectively for the first course of treatment; the predicted plasma concentrations based on a one-compartment model are also indicated. Decay curves based on plasma ultrafiltrate and urinary excretion rate data are shown in Fig. 2. The first (solid) part of each curve is the line of best fit to the postinfusion plasma ultrafiltrate data. The second (broken) part of each

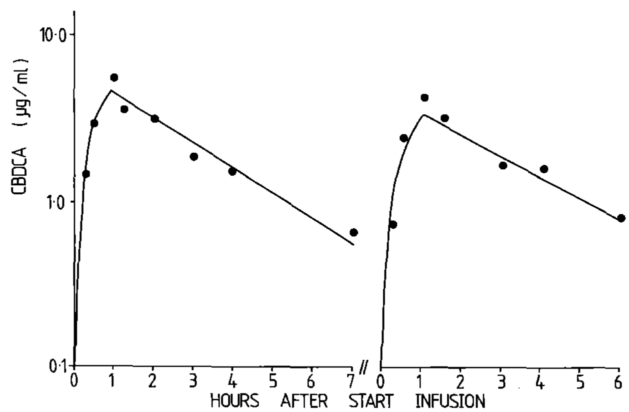

Fig. 1. CBDCA plasma levels recorded *(points)* in patient 4, day 1 and day 3 respectively of the first course. *Solid line,* predicted plasma concentrations based on compartmental analysis of the data

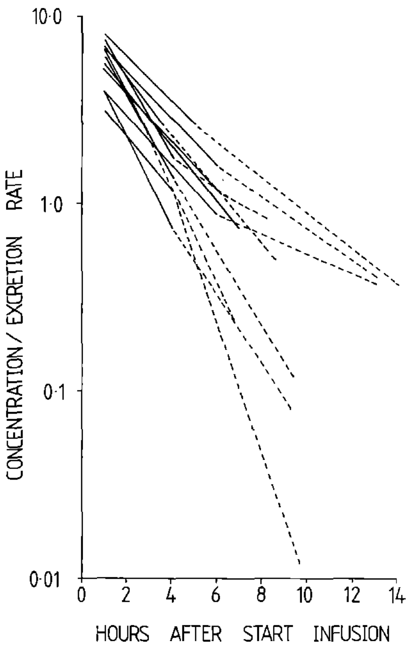

Fig. 2. Comparison of decay curves for CBDCA based on postinfusion plasma ultrafiltrate data (——) and urinary excretion rate data (- - - -) for five patients on day 1, and six patients on day 3

is the line of best fit to the urinary excretion rate data, the intercept of which was positioned to correspond to the end of the corresponding plasma data. The slope of the original plot was maintained. Although plasma ultrafiltrate concentrations were only measurable for up to 6–7 h after infusion, the urinary excretion rate data confirmed the mono-exponential decay of carboplatin concentrations for up to 14 h after infusion.

Individual values of pharmacokinetic parameters are shown for each patient in Table 1. There was considerable interpatient variability in the parameters. Renal clearance of carboplatin contributed to approximately 58.4% of the total clearance of the drug in these patients. Mean renal clearance was approximately equal to creatinine clearance. Only one patient (patient 5), showed possible evidence of active tubular secretion of the drug. This patient excreted 88.2% of the carboplatin dose into the urine over the 24-h period after the start of the infusion. Where comparisons were possible within patients, the carboplatin half-life was similar whether determined from plasma ultrafiltrate levels or from the urinary excretion rate data.

Compartmental estimates of clearance, volume of distribution and half-life were comparable with those determined by non-compartmental methods for both days of treatment (Table 1). However, the estimates did differ significantly ($P < 0.05$), primarily due to uniformly lower estimates of half-life by the compartmental method. The absolute difference was relatively small, however (e.g., 5% for clearance), and was unlikely to be of general significance. The non-compartmental approach would be preferable for future studies, in view of the relative ease and speed of the calculations involved. Compartmental analysis would be desirable where prediction of plasma level – time profiles was required for different infusion schedules.

There were no significant differences between pharmacokinetic parameters for carboplatin determined on days 1 and 3 of treatment in each patient (Table 1).

Table 1. Patient characteristics and pharmacokinetic parameters for carboplatin

Patient no.	Sex/age (yr)	Surface area (m²)	Creatinine clearance (ml min⁻¹ m⁻²)		Clearance				Renal Clearance Non-compartmental (ml min⁻¹ m⁻²)		Volume of Distribution				Half-life (p)[a]				Half-life (u)[b] (min)		Dose excreted in 24 h (%)	
					Non-compartmental (ml min⁻¹ m⁻²)		Compartmental (ml min⁻¹ m⁻²)				Non-compartmental (l/m²)		Compartmental (l/m²)		Non-compartmental (min)		Compartmental (min)					
			Day 1	Day 3	Day 1	Day 3	Day 1	Day 3	Day 1	Day 3	Day 1	Day 3	Day 1	Day 3	Day 1	Day 3	Day 1	Day 3	Day 1	Day 3	Day 1	Day 3
1	M/72	1.75	86.3	76.6	99.9	98.5	110	103	62.8	69.3	13.9	13.7	11.8	10.3	80.4	84.0	74.1	69.2	70.4	128	62.8	70.4
2	M/69	1.85	53.6	67.0	64.4	56.1	69.6	59.4	46.2	–	15.0	13.2	12.2	11.9	141	151	121	138	–	177	72.4	–
3	M/74	1.70	29.2	27.3	87.4	85.9	95.2	81.2	19.7	16.9	11.9	19.3	8.65	12.5	83.6	142	63.0	106	88.4	173	22.6	19.6
4	M/44	1.75	48.2	50.4	104	119	109	124	65.3	74.8	21.0	26.2	18.1	26.9	123	133	115	150	93.9	210	62.9	63.0
5	M/59	1.80	72.8	77.2	185	165	187	214	163	99.6	24.2	32.7	18.2	35.7	72.4	116	67.3	116	85.8	62.8	88.2	60.3
6	M/75	1.60	18.8	19.1	122	123	129	136	50.6	–	18.1	25.0	15.3	20.7	91.7	128	82.0	106	–	–	41.7	–
7	F/57	1.70	136	108	71.7	81.8	80.1	95.1	41.9	30.9	17.3	13.6	13.2	10.5	145	107	114	76.5	198	120	58.4	37.8
Mean	64	1.74	63.6	60.8	105	104	111	116	64.3	58.3	17.3	20.5	13.9	18.3	105	123	91.0	109	107	145	58.4	50.2
SD	11	0.08	39.5	31.0	40.4	35.3	38.8	50.0	44.1	33.8	4.2	7.65	3.49	9.85	30.4	22.8	25.0	29.6	51.7	52.3	21.2	21.0

[a] Half-life determined from plasma ultrafiltrate data
[b] Half-life determined from urinary excretion rate data

Discussion

Carboplatin disposition in patients with small cell lung cancer was clearly defined by the application of a sensitive and specific high-performance liquid chromatographic assay for the unchanged drug. The analytical method differed from those already published [6, 8] in that a sample clean-up step was introduced prior to chromatography. This lowered the detection limits of the assay by removing interfering peaks and allowed levels of carboplatin to be reproducibly quantitated during and for up to 6 h, or approximately three half-lives, after a 1-h infusion of 100 mg/m^2 of the drug. Reliable estimates of the terminal half-life could therefore be obtained. These estimates were confirmed using urinary excretion rate data.

The mean carboplatin half-life (105 min) in the present study was similar to that obtained by Harland et al. [8] (90 min) in patients with advanced cancer to whom a dose of 300–500 mg/m^2 was administered by 1-h infusion. Harland et al. did not publish values of total and renal clearance for unchanged drug. The percentage of the dose recovered unchanged in urine over 24 h in the present study was 58.4% as against 32% reported by Harland et al. However, chemical reaction with urinary constituents may have resulted in the reduced recovery they report, since total platinum recovery was 65% in their study. This value was comparable with that reported by Calvert et al. [1], who recovered 67%±2% of the administered carboplatin dose in urine, and that reported by Koeller et al. [11], who recovered 65.7% of the administered dose. Comparison with other pharmacokinetic studies was difficult, since only total ultrafilterable platinum in plasma was measured in these studies [1–4, 11, 18]. However, Gaver and Deeb [6] have suggested that ultrafilterable platinum after carboplatin administration consists almost entirely of unchanged drug, with irreversible binding to plasma proteins comprising the remaining platinum fraction in plasma. If this is established then ultrafilterable platinum levels may be a useful guide to unchanged carboplatin levels in plasma. Koeller et al. [11] reported a mean half-life of 131 min for ultrafilterable plasma platinum after carboplatin infusion. Comparable vlaues have been reported by Curt et al. [2] (170 min), Harland et al. [8] (96 min), and Van Echo et al. [18] (102 min). These values were similar to those described for unchanged carboplatin in the present study and in the study of Harland et al. [8]. The mean total-body clearance of ultrafilterable plasma platinum was reported to be 53.6 ml min^{-1} m^{-2} by Koeller et al. [11], and approximately 60 ml min^{-1} m^{-2} by Curt et al. [2] and Van Echo et al. [18]. These values were considerably lower than that found for unchanged carboplatin in the present study and may reflect the presence of other low-molecular-weight species in plasma ultrafiltrates, which would result in higher levels and hence a lower estimate of clearance. The mean steady-state volume of distribution of ultrafilterable platinum was reported by other authors as 16.0 l/m^2 [11, 18], which was similar to that found for unchanged drug (17.3 l/m^2) in the present study.

Correlations between ultrafilterable platinum clearance and creatinine clearance have been reported in patients with renal impairment after carboplatin [3, 4, 8] and iproplatin [13] administration, though not after cisplatin administration [16]. Egorin et al. [3, 4] have shown that carboplatin dosage can be predicted for patients with renal impairment based on predose knowledge of creatinine clearance, surface area, pretreatment platelet count, desired platelet nadir and status of prior chemotherapy. Correlations beween creatinine clearance and total or renal clearance, or the percentage of the dose excreted have not been reported for unchanged carboplatin. This possibility was examined in the present study by considering the data from day 1 and day 3 collectively. With the inclusion of patient 7, who had high creatinine clearance (136, 108 ml min^{-1} m^{-2} respectively for days 1 and 3), there were no significant relationships between total clearance, renal clearance or percentage of the dose excreted and creatinine clearance. However, when the data for this patient were excluded from the calculations there was a highly significant relationship between creatinine clearance and the percentage of the dose excreted ($r^2=0.555$; $P=0.0134$) and a reasonable relationship with renal clearance ($r^2=0.386$; $P=0.0554$), but no relationship with total clearance ($r^2=0.03$, $P=0.592$). The last observation may be a result of the non-renal clearance component, which contributes to total clearance and is probably determined by the rate of chemical reaction of carboplatin with proteins and low-molecular-weight reactants, rather than kidney function. This contribution may be less important for estimates of total clearance made from ultrafilterable platinum levels, which probably include a contribution from low-molecular-weight platinum metabolites.

There was no evidence of alterations in carboplatin elimination between days 1 and 3 of the first course in this study. This was not surprising, since carboplatin has not been shown to be a significant nephrotoxin and the present studies were conducted in only the first course of therapy. We have recently shown that repeated administration of cisplatin results in reduced renal elimination of the drug [15], probably as a result of impaired renal tubular secretion. In the case of carboplatin there is little evidence at present for active secretion, since renal clearance is similar to glomerular filtration rate [3, 4, 8]. However, it is possible that carboplatin undergoes renal tubular reabsorption in parallel with active tubular secretion, the net result being a level of renal clearance which approximates the glomerular filtration rate. The possibility of changes in carboplatin renal clearance with repeated courses of treatment requires further study.

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