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The disposition of carboplatin in ovarian cancer patients*

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Summary. Carboplatin was given as a 30-min infusion to 11 ovarian cancer patients at doses of 170–500 mg/m^2. The ages, weights, and creatinine clearances (Cl_{cr}) ranged from 44 to 75 years, from 44 to 74 kg, and from 32 to 101 ml/min, respectively. Plasma, plasma ultrafiltrate (PU), and urine samples were obtained at appropriate times for 96 h and were analyzed for platinum. The PU and urine were also analyzed for the parent compound by HPLC. In patients with a Cl_{cr} of about 60 ml/min or greater, carboplatin decayed biexponentially with a mean $t_{½\alpha}$ of 1.6 h and a $t_{½\beta}$ of 3.0 h. The mean (± SD) residence time, total body clearance, and apparent volume of distribution were 3.5 ± 0.4 h, 4.4 ± 0.85 l/h, and 16 ± 3 l, respectively. C_{max} and AUC_{inf} values increased linearly with dose, and the latter values correlated better with the dose in mg than in mg/m^2. No significant quantities of free, ultrafilterable, platinum-containing species other than the parent compound were found in plasma, but platinum from carboplatin became protein-bound and was slowly eliminated with a minimal $t_{½}$ of 5 days. The major route of elimination was excretion via the kidneys. Patients with a Cl_{cr} of 60 ml/min or greater excreted 70% of the dose as the parent compound in the urine, with most of this occurring within 12–16 h. All of the platinum in 24-h urine was carboplatin, and only 2%–3% of the dosed platinum was excreted from 48 to 96 h. Patients with a Cl_{cr} of less than about 60 ml/min exhibited dose-disproportional increases in AUC_{inf} and MRT values. The latter were inversely related to Cl_{cr} ($r = -0.98$). Over a dose range of 300–500 mg/m^2, carboplatin exhibited linear, dose-independent pharmacokinetics in patients with a Cl_{cr} of about 60 ml/min or greater, but dose reductions are necessary for patients with mild renal failure.

Introduction

Carboplatin, *cis*-diammine [1,1 cyclobutane dicarboxylato(2-)-0,0']platinum(II) (CBDCA, JM8, NSC 241240, Paraplatin), is a second generation, platinum-containing antitumor agent. It was selected for clinical evaluation based on its experimental antitumor and toxicologic profiles in animal models that demonstrated it to be less nephrotoxic and less emetic than cisplatin (Platinol). These profiles have recently been reviewed by Rose and Schurig [14].

Carboplatin is active in ovarian cancer, small-cell lung cancer, testicular cancer, and head and neck cancer. Clinical investigations, including phase II and phase III studies, are actively under way in the United States and overseas. The phase I clinical data have recently been reviewed by Calvert et al. [2]. The advantage of carboplatin over cisplatin is that the former does not cause meaningful renal toxicity even when given without added hydration. Relative to cisplatin, it causes less severe and shorter lasting nausea and vomiting that appear to be more amenable to treatment with antiemetics. In addition, carboplatin does not cause the neurotoxicity that becomes dose-limiting when large doses of cisplatin are given with hypertonic saline to prevent nephrotoxicity. The usual dose-limiting toxicity of carboplatin is myelosuppression, particularly thrombocytopenia.

Several investigators have reported on the plasma concentrations of free or total platinum in cancer patients after the administration of carboplatin [1, 4, 5, 9, 10, 16, 17]. However, only Harland et al. [9] have reported concentrations of the parent compound in the plasma ultrafiltrate and urine. According to the results of Calvert et al. [1] and Harland et al. [9], the primary route of excretion is via the kidneys, with about 70% of the dosed platinum being excreted in 24-h urine. However, only about 32% of the parent compound has been recovered in 24 h urine [9]. The total body clearance and renal clearance of free, ultrafilterable platinum have been correlated with the glomerular filtration rate [5, 9], and Egorin et al. [5] have reported a relationship between the percentage of reduction in platelet counts and the area under the plasma concentration vs time curve (AUC).

The purpose of this study was to define the disposition of the parent compound, free ultrafilterable platinum, and protein-bound platinum in cancer patients after the administration of therapeutic doses of carboplatin based on validated HPLC and atomic absorption spectrophotometric procedures for carboplatin and platinum, respectively.

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Materials and methods

Study design. The 11 patients studied were part of an open, nonrandomized clinical study designed to determine the efficacy of carboplatin as a second-line therapy for ovarian cancer [3]. The patients had measurable or evaluable advanced epithelial cancer and had previously been treated with cisplatin. They received no radiation therapy within 4 weeks of initiation of the study and had no involvement of the bone marrow or liver. Their ages, weights, and creatinine clearances ranged from 44 to 75 years, 44 to 74 kg, and 32 to 101 ml/min, respectively (Table 1). Written informed consent was obtained. Creatinine clearances, calculated from a 24-h urine sample and a serum creatinine value, were determined within 2 weeks of the start of the study. Patients were fasted overnight and drank 335 ml water 1 h before drug administration. Carboplatin (170–500 mg/m^2) was given i.v. over 30 min, and blood and urine samples were obtained at various times for 96 h. Complete blood cell and platelet counts were obtained weekly.

Drug. The dose of carboplatin (Bristol-Myers Co., Syracuse, NY) was given in 160 ml 5% dextrose over 30 min via an IVAC (IVAC Corp., San Diego, Calif.) constant-rate infusion pump. A portion of the dosing solution was frozen in dry ice and was later analyzed to determine the exact amount of carboplatin given.

Sample collection and processing. Blood samples (10 ml) were drawn by venipuncture or through indwelling catheter immediately before drug administration (0 time) and at the following times after the start of the infusion: 15, 30, 45, and 60 min, 1.5, 2, 4, 6, 8, 10, 12, 14, 24, 48, 72, and 96 h. The blood was placed in Vacutainer tubes containing EDTA, mixed, and immediately centrifuged for 15 min (1000 *g*) at 5° C. The plasma layer was removed and samples were immediately placed into Amicon Centrifree micropartition units (Amicon Corp., Danvers, Mass.). The plasma ultrafiltrate (PU) was generated by centrifugation at 200 *g* for 20 min. The PU and the remaining plasma were frozen in a dry ice/ethanol bath and placed into dry ice. Samples were shipped in dry ice and stored at −60° C until analyzed for carboplatin.

Control urine (0 time) was obtained prior to drug administration. Total urine output was collected over the following intervals, beginning at the start of the infusion: 0–4, 4–8, 8–12, 12–16, 16–24, 24–48, 48–72, and 72–96 h. The urine was stored in a refrigerator during the collection interval. At the end of the interval, the patient was asked to void, the urine for that interval was mixed, and the volume was determined. Duplicate urine samples (5 ml) were transferred to tubes, placed into dry ice for shipment, and stored at −60° C until analyzed for carboplatin.

Quality control samples of carboplatin in control plasma, PU, and urine were prepared at the study site on each dosing day. These samples were shipped, stored, and analyzed along with the patient samples.

Carboplatin analysis. Plasma ultrafiltrate (PU) and urine samples were analyzed for carboplatin by previously described HPLC methods [6] within 1 week of sample collection. Quality control samples were analyzed with each analytical run. The mean (± SD) slope for the standard curves of carboplatin in the PU was 234 ± 54 (n = 14), and the correlation coefficient was ⩾0.998. Each standard curve was based on a minimum of six standards in duplicate, covering a range of 1–50 μg/ml. With the quality control samples of 5 and 25 μg carboplatin/ml PU, within-day errors were 9% and 7%, respectively. The corresponding between-day errors were 6% and 5%, and the mean accuracy (n = 14) was 102% and 101%, respectively.

The mean (± SD) slope for the standard curves of carboplatin in human urine was 470 ± 63 (n = 15), and the correlation coefficient was ⩾0.997. Seven standards in duplicate, covering a range of 5–500 μg carboplatin/ml urine, were prepared for each standard curve. Quality control samples of 50, 150, and 300 μg carboplatin/ml gave between-day and within-day errors of 4% or less. The mean accuracy for the determinations was 99% (n = 15), 99% (n = 15), and 101% (n = 13), respectively, for the three concentrations. Based on this data, the analyses for carboplatin in the PU and urine were accurate, precise, and reproducible.

Platinum analysis. The urine, PU, and plasma were analyzed for total platinum by flameless atomic absorption spectrophotometry (AA) with a Varian model AA1475 atomic absorption spectrophotometer (Varian Instruments, Sunnyvale, Calif.) equipped with a model GTA-95 graphite tube atomizer and an automatic sample dispenser. For the PU and urine, the sample dispenser was pro-

Table 1. Demographic data for ovarian cancer patients entered into the pharmacokinetic study

Patient no.	Age (y)	Height (cm)	Weight (kg)	S.A. (m^2)	Dose		Creatinine clearance (ml/min per 1.73 m^2)
					mg	mg/m^2	
1	44	168	53.8	1.60	666	416	81
2	55	163	61.5	1.66	380	229	33
3	52	167	73.5	1.82	738	405	96
4	75	160	68.1	1.71	301	176	32
5	60	148	52.5	1.45	728	502	93
6	52	156	50.3	1.47	433	294	116
7	72	169	53.5	1.60	598	374	66
8	67	173	56.7	1.67	507	304	93
9	51	160	59.0	1.60	350	219	52
10	68	164	47.8	1.50	413	275	63
11	47	161	44.5	1.43	240	168	69

grammed to create five standards covering the range of 0.2–1.9 μg equivalent (equiv) carboplatin/ml. The total volume injected was 20 μl for blanks, standards, and samples. The hollow, platinum cathode lamp was operated at 9 mA. Background correction was achieved with a deuterium lamp. Ashing and atomization temperatures were 1200° C and 2800° C, respectively. The monochrometer wavelength (265.9 nm) was specific for platinum and had a spectral band width of 0.2 nm. The same conditions were applied for plasma, except that the plasma samples were diluted 1:4 with 0.05% Triton X-100 and the range of the standard curve was 0.4–9.5 μg equiv carboplatin/ml. Quality control samples were included in each analytical run.

For the analysis of platinum in urine, quality control samples containing 10, 150, and 300 μg carboplatin/ml gave between-day errors of 8%, 3% and 8%, respectively. The within-day error at 150 μg/ml was 4%. The mean accuracy was 102% (n = 11), 101% (n = 13), and 96% (n = 13) for the three concentrations. For the analysis of platinum in the PU, quality control samples containing 0.5, 5.0, and 25 μg carboplatin/ml gave between-day errors of 4%, 6%, and 7%, respectively. The mean accuracy was 100% (n = 8), 105% (n = 12), and 100% (n = 19) for the three concentrations. Finally, for the analysis of total platinum in the plasma, quality control samples of 5 and 25 μg carboplatin/ml gave mean between-day errors of 7%. Within-day errors were 6% and 5%, and the mean accuracy was 102% (n = 14) and 100% (n = 13), respectively. Based on these results, the AA procedures for platinum in the PU, urine and plasma were accurate, precise, and reproducible.

Calculations. The output of the detector for the HPLC analyses of carboplatin was fed directly into a laboratory sample management package operating in a Hewlett Packard model HP3357 laboratory automation system (Hewlett Packard Co., Palo Alto, Calif.). The absorbance data from the AA analyses for total platinum were hand-entered into the system. A computer program employing Statistical Analysis System (SAS) software (SAS Institute Inc., Cary, NC) calculated all standard curve parameters, sample and quality control values, intra- and interassay variability of quality control samples, and pharmacokintic parameters and tabulated and plotted the data. The within- and between-day variability for the quality control samples was calculated by the SAS VARCOMP procedures with the MINQUEO option. If the predicted concentration of a sample was less than the lowest standard or greater than 110% of the highest standard, the value was deleted.

The regression of the weighted (1/concn) peak height of carboplatin in the PU and urine vs the concentration of carboplatin in the standards was calculated by least-squares linear regression analysis, and the concentration of carboplatin in the samples was estimated by inverse prediction [11]. Outliers were evaluated by the method of Prescott [12].

For the AA analysis of platinum in the urine, PU, and plasma, the standard and sample results were expressed as μg equiv carboplatin/ml instead of μg platinum/ml. In this way the results could be directly compared to the amounts of carboplatin found by HPLC analysis. The AA data for platinum standards was fitted with a nonlinear model relating the concentration to absorbance by the following equation:

$$\text{Absorbance} = A + B \cdot \text{concn}^C, \quad (1)$$

where A, B, and C are parameters unique to each standard curve. The concentration of platinum in the samples was calculated by inverse prediction.

Plasma concentration (C) vs time (t) data were analyzed by noncompartmental methods [8, 13]. The observed peak plasma concentrations (C_{max}) and the time of occurrence (t_{max}) were tabulated. The best-fit, terminal log-linear portion of the data was determined by least-squares linear regression analysis [15] of the data. The data was fit to the function

$$\ln C = \ln B - bt, \quad (2)$$

starting with the last three data points for which $C > 0$. The last point at which $C > 0$ was defined as point n. This procedure continued adding preceding data points one at a time, until the time of 2 h (point m) was reached. The terminal log-linear portion was then defined as that portion yielding the smallest mean-square error. The slope (b) of this portion was used to determine the half-life ($t_{½}$) by the following equation:

$$t_{½} = \ln 2/b \quad (3)$$

The areas under the C vs t (AUC) and the t·C vs t (AUMC) curves were calculated using the trapezoidal rule. The AUC and AUMC to point m were calculated using the linear trapezoidal rule, and in the log-linear portion, from point m to point n, by the log trapezoidal rule as suggested by Reigelman and Collier [13].

The mean residence time (MRT) in the body was calculated by the following equation [8]:

$$\text{MRT} = \text{MRT}_{inf} - T/2 = \frac{\text{AUMC}_{inf}}{\text{AUC}_{inf}} - T/2, \quad (4)$$

where T is the infusion time in h.

The total body clearance (Cl_{Tb}) was calculated by dividing the dose of carboplatin in mg by the AUC_{inf}. The apparent volume of distribution at steady state (Vss) was calculated by the following relationship [8]:

$$\text{Vss} = \frac{\text{infused dose} \cdot \text{AUMC}_{inf}}{(\text{AUC}_{inf})^2} - \frac{\text{infused dose} \cdot T}{2\,\text{AUC}_{inf}}, \quad (5)$$

where T is the infusion time.

The renal clearance (Cl_r) was calculated by dividing the mg excreted in the urine by the AUC_{inf}. Nonrenal clearance (Cl_{nr}) was obtained by subtracting the renal clearance from the total body clearance:

$$Cl_{Tb} = Cl_r + Cl_{nr} \quad (6).$$

Results

Carboplatin

The C_{max} values for carboplatin occurred at the end of the infusion (0.5 h) in 9 of the 11 patients (Table 2). In two patients (nos 7 and 8), the C_{max} values occurred at 0.75 h. There was a linear increase in C_{max} values with increasing dose, whether the dose was expressed in mg/m^2 (r = 0.92) or in mg (r = 0.90). This linear relationship between the C_{max} and the dose (Fig. 1) also appeared to hold for the patients (nos. 2, 4, and 9) with creatinine clearances of <60 ml/min. At a dose of 400 mg/m^2, the peak plasma concentration of carboplatin was about 50 μg/ml.

Table 2. Pharmacokinetic parameters for carboplatin in plasma ultrafiltrate after the administration of carboplatin to cancer patients

Patient no.	Cl_{cr} (ml/min)	C_{max} (μg/ml)	$t_{1/2}$ (h)		AUC_{inf} (μg/ml · h)	MRT (h)	Vss (l)	Clearances (l/h)			Percentage of dose in urine (0–48 h)
			α	β				Cl_{Tb}	Cl_r	Cl_{nr}	
4	32	22	3.1	5.6[c]	117	7.2	18.4	2.57	1.21	1.36	47
2	32	28	2.0	5.1	147	7.0	18.1	2.58	0.843	1.74	33
9	48	22	1.3	3.8	83	5.0	21.2	4.21	1.72	2.49	41
10	55	40	1.5	2.2	90	3.0	13.8	4.58	2.54	2.04	55
11*	57	23	2.2	2.6	78	3.7	11.3	3.06	1.62	1.44	53
7	61	42[a]	2.0	–	119	3.0	15.1	5.02	–	–	[b]
1	75	71	1.6	3.2	176	3.5	13.3	3.78	2.82	0.96	74
5*	78	63	1.4	3.2	153	3.7	17.7	4.76	3.72	1.04	78
8*	90	39[a]	1.7	2.6	116	3.4	14.8	4.37	2.84	1.53	65
6	99	32	1.1	5.9	71	4.0	24.2	6.12	4.04	2.08	66
3	101	52	1.8	3.3	178	3.8	15.8	4.15	3.02	1.13	73

[a] t_{max} = 0.75 h, others 0.5 h
[b] 69% in 16 h; 16–24 h urine lost
[c] A $t_{1/2\gamma}$ of 13 h was observed with this patient
* Second course of treatment, all others were first course

In the nine patients with creatinine clearances (Cl_{cr}) of about 50 ml/min or greater, the plasma concentrations of carboplatin decayed in a biexponential fashion, with the exception of one patient (no. 7) in whom the decay was monoexponential ($t_{½}$ = 2 h). The mean (± SD) $T_{½\alpha}$, calculated from 0.5 to 2 h, was 1.6 ± 0.3 h (n = 9), and the mean (± SD) $t_{½\beta}$, calculated from 2 to 14 h, was 3.0 ± 0.5 h (n = 7). The mean harmonic $t_{½\beta}$ was 3.1 h. One patient (no. 6) had a mean $t_{½\beta}$ of 5.9 h that was greater than 2 SD from the mean for eight patients, and this value was excluded in calculating the mean $t_{½\beta}$. In the two patients with a Cl_{cr} of 32 ml/min (nos. 4 and 2), the beta half-lives were > 5 h, and in one (no. 4) carboplatin decayed in a triphasic manner, with a $t_{½\gamma}$ of 13 h. The plasma half-lives of carboplatin, therefore, were markedly increased in the two patients with a Cl_{cr} of 32 ml/min.

The AUC for carboplatin, from 0 time to infinity (AUC_{inf}), increased linearly with the dose in patients with a Cl_{cr} of 60 ml/min or greater (Fig. 2). In patients with a Cl_{cr} of <60 ml/min, the AUC_{inf} values were disproportionally higher than in the other patients. This is illustrated by patients 2 and 5, who each had AUC_{inf} values of about 150 μg/ml·h (Table 2). The former (Cl_{cr} = 32 ml/min) received a dose of 380 mg (229 mg/m²), whereas the latter (Cl_{cr} = 78 ml/min) was given a dose of 728 mg (502 mg/m²). The best correlation between the AUC_{inf} and the dose was found when the dose was expressed in mg (r = 0.92, P = 0.01):

$$AUC_{inf} = 0.31 \text{ dose (mg)} - 54. \quad (7)$$

The relationships between the AUC_{inf} and the dose were poorer (r < 0.80) when the dose was expressed as mg/m² or mg/kg.

The mean (± SD) residence time (MRT) for carboplatin, or the time for 63.2% of the dose to be eliminated from the plasma, was 3.5 ± 0.4 h and relatively constant in the eight patients with a Cl_{cr} of about 60 ml/min or greater. In one patient with a Cl_{cr} or 48 ml/min, the MRT was 5.0 h, whereas in the two patients with a Cl_{cr} of 32 ml/min, the MRT values (7.0 and 7.2 h) were twice those seen in pa-

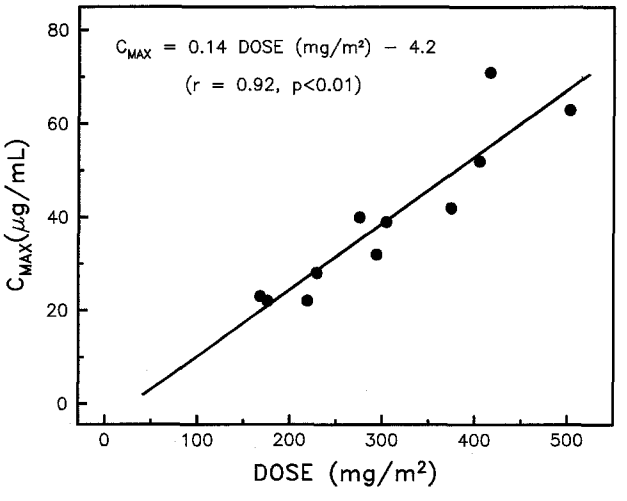

Fig. 1. Relationship between carboplatin C_{max} valaues (μg/ml) and the dose of carboplatin in mg/m² in ovarian cancer patients following a 30-min i.v. infusion

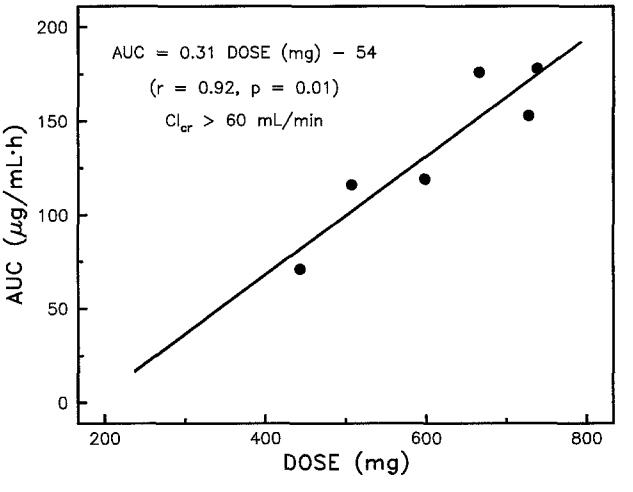

Fig. 2. Relationship between AUC_{inf} values for carboplatin and the dose in mg in ovarian cancer patients with creatinine clearances of >60 ml/min. The doses were given i.v. over 30 min

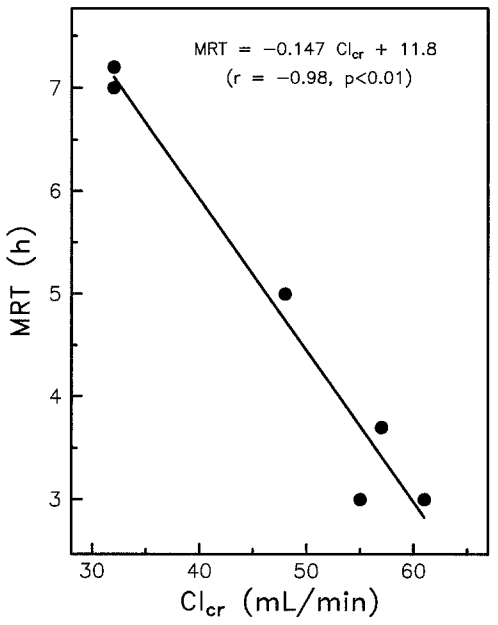

Fig. 3. Relationship between the mean residence time (*MRT*) for carboplatin and the creatinine clearance (Cl_{cr}) in ovarian cancer patients with a Cl_{cr} of about 60 ml/min or less given carboplatin as a 30-min i.v. infusion

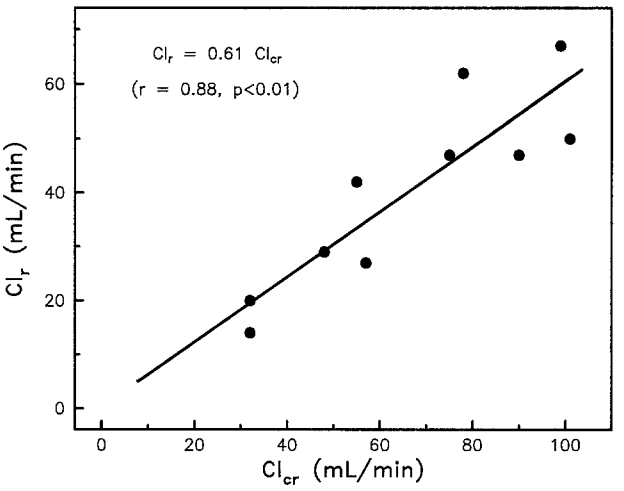

Fig. 4. Relationship between the renal clearance (Cl_r) of carboplatin and the creatinine clearance (Cl_{cr}) in ovarian cancer patients given carboplatin as a 30-min i.v. infusion. The doses ranged from 170 to 500 mg/m^2

tients with a Cl_{cr} of about 60 ml/min or greater. For patients with a Cl_{cr} of between 30 and 60 ml/min, the MRT values for carboplatin were inversely related ($r = -0.98$, $P < 0.01$) to Cl_{cr} (Fig. 3):

$$MRT = -0.147\ Cl_{cr}\,(ml/min) + 11.8 \quad (8)$$

The mean (± SD) apparent volume of distribution at steady state (Vss) for carboplatin was 16 ± 3 l ($n = 10$). Patient no. 6 was excluded from the calculation of the mean, since she was the only patient with clinically apparent ascites. The latter probably accounted for her larger Vss (Table 2).

The mean (± SD) total body clearance (Cl_{Tb}) of carboplatin in nine patients was 4.4 ± 0.85 l/h. In the two patients (nos. 2 and 4) with a Cl_{cr} of 32 ml/min, the Cl_{Tb} was only 2.6 l/h.

The renal clearance (Cl_r) of carboplatin was linearly related to the Cl_{cr} (Fig. 4). When the clearances were expressed in ml/min, the relationship ($r = 0.88$, $P < 0.01$) was defined by the following equation:

$$Cl_r = 0.61\ Cl_{cr}. \quad (9)$$

The mean nonrenal clearance for carboplatin was 1.58 ± 0.5 l/h, or 26 ml/min (Table 2).

Free platinum

The C_{max} values for plasma, free platinum occurred at the same time and were in good agreement with the C_{max} values for carboplatin. The mean (± SD) ratio of carboplatin C_{max}/free platinum C_{max} was 1.06 ± 0.099 ($n = 11$). This agreement between free platinum and carboplatin plasma concentrations held out to the times when carboplatin could no longer be measured. The mean (± SD) ratio of the AUC for carboplatin and free platinum out to the time of the last measurable concentration of carboplatin (1 μg/ml) was 0.99 ± 0.081 ($n = 10$). This concentration of carboplatin occurred between 10 and 14 h in all of the patients except the two with a Cl_{cr} of 32 ml/min, when the last measurable value was at 24 h. The mean (± SD) ratio of AUMC values (carboplatin/free platinum) out to the last measurable carboplatin concentration was 1.0 ± 0.12 ($n = 10$). These results show that, over the time period when carboplatin could be quantitated, all of the free, non-protein-bound platinum in plasma was present as carboplatin.

Protein-bound platinum

The concentrations of bound platinum were obtained by subtracting the values for free platinum in the PU from the values for total platinum (free plus bound) in plasma. The mean (± SD) terminal half-life for bound platinum, measured from 24 to 96 h, was 5.3 ± 2.5 days ($n = 9$). A half-life could not be calculated for patient no. 3 (no plasma samples beyond 24 h), and patient 11 had a half-life (18.7 days) that was greater than 2SD from the mean of all values. At 96 h, all of the patients had bound platinum concentrations of 0.7–2.5 μg carboplatin equiv/ml plasma.

The true half-life for bound platinum is probably longer than 5.3 days. Two (nos. 5 and 11) of the three patients (nos. 5, 8 and 11) who received an initial dose of carboplatin approximately 1 month before the study dose had plasma concentrations of 0.4 and 0.5 μg carboplatin equiv/ml in their predose plasma samples. All of the other patients, including no. 8, had total platinum values of less than the lower limit of the assay (0.5 μg carboplatin equiv/ml) in their predose plasma samples. Since bound platinum probably represents a mixture of compounds that reacted with the platinum from carboplatin (e.g. proteins, nucleic acids, nucleosides, sulfhydryl compounds), the calculation of other pharmacokinetic parameters was not appropriate.

Urinary excretion

A mean (± SD) of 71% ± 5.7% of the dose was excreted as carboplatin in the urine in 48 h by patients ($n = 5$) with a Cl_{cr} of about 60 ml/min or greater. The patients with a Cl_{cr} of 48, 55, and 57 ml/min excreted 41%, 55%, and 53%, respectively, of the dose in the urine as carboplatin, where-

as the patients with a Cl_{cr} of 32 ml/min excreted 33% (no. 2) and 47% (no. 4) in the urine as carboplatin (Table 2). The urinary excretion of carboplatin was rapid, with most being excreted by 12–16 h. Carboplatin was detected in the 24- to 48-h urine samples of only two patients (nos. 2 and 5) and accounted for about 3% of the dose. The major route of elimination of carboplatin was via the kidneys, and the amounts recovered in the urine decreased when Cl_{cr} fell below about 60 ml/min.

In 48 h, a mean (± SD) of 70% ± 4.7% of the dose of platinum was excreted in the urine by the patients (n = 5) with a Cl_{cr} of 60 ml/min or greater. The three patients with a Cl_{cr} of 48, 55, and 57 ml/min excreted a mean (± SD) of 56% ± 2.2% of the dose of platinum in 48 h; the two patients with a Cl_{cr} of 32 ml/min excreted 36% and 54% of the platinum in 48 h (Table 3). In the ten patients with 24-h urine samples (no. 7 excluded), the mean (± SD) ratio of the percentage of the dose excreted as carboplatin in 24 h divided by the percentage of the dose excreted as platinum in 24 h was 1.0 ± 0.083. Therefore, all of the platinum excreted in the urine in 24 h was present as carboplatin, irrespective of the degree of renal impairment.

An additional 2%–3% of the dose of platinum was excreted in the urine of all patients between 48 and 96 h post-administration. Platinum (0.5 μg equiv/ml or less) was detected in the 0-time urines of each of the three patients (nos. 5, 8 and 11) given carboplatin about 4 weeks prior to receiving this dose. All of the 0-time urines from the other patients, except that from no. 9 (0.3 μg equiv/ml), had platinum concentrations below the lower limit of quantitation (0.2 μg equiv/ml). Examination of the cumulative percentage excreted vs time plots indicated that platinum may be excreted in the urine beyond 96 h.

Discussion

With the exception of the paper by Harland et al. [9], who analyzed for carboplatin by HPLC, all of the published data on the pharmacokinetics of carboplatin are based on AA analysis of either free platinum in PU or of total platinum in plasma [1, 4, 5, 9, 10, 16, 17]. The latter measures free plus bound platinum species and is not specific for the parent compound. Results from the analysis of free platinum in the PU may or may not be a valid measurement of carboplatin concentrations, depending on how rapidly the plasma and PU were generated after the blood was drawn from the patient. This is because carboplatin has been reported to have limited stability in human plasma [6, 7]. The validity of the HPLC analysis of carboplatin in PU is also dependent on the rapid generation of plasma and PU. In addition, since carboplatin has limited stability in PU [6], valid results require that samples be stored frozen and analyzed within 1 week of preparation. Differences between the pharmacokinetics of carboplatin reported here and the published data from other laboratories can be attributed to differences in the assay specificity, the time between blood withdrawal and preparation of the PU, the storage conditions, and the time between sample preparation and analysis. Our results are based on specific and validated methods for the analysis of the parent compound in the PU and urine and are further supported by the results from quality control samples prepared in each matrix at the study site on the day of dose administration.

Using an HPLC procedure, Harland et al. [9] have followed the plasma concentrations of carboplatin in four cancer patients for about 5 h. After doses of 300, 400, and 500 mg/m^2, they reported a mean (± SD) $T_{½\alpha}$ of 1.50 ± 0.01 h for carboplatin that is in good agreement with our mean $t_{½\alpha}$ value of 1.6 ± 0.3 h for nine patients. However, in our study carboplatin concentrations remained above the lower limit of quantitation (1 μg/ml) for 10–14 h in patients given doses of 300–500 mg/m^2, and an additional beta phase with a mean (± SD) half-life of 3.0 ± 0.5 h (n = 7) was observed. The half-life of carboplatin, therefore, is longer than previously reported.

Harland et al. [9] have also reported that most, if not all, of the plasma, free platinum during the initial phase was in the form of carboplatin. Our results confirm and extend this conclusion into the beta phase. All of the plasma, free platinum was present as carboplatin out to the

Table 3. Pharmacokinetic parameters for free platinum in plasma ultrafiltrate after the administration of carboplatin to cancer patients[a]

Patient no.	Cl_{cr} (ml/min)	C_{max} (μg/ml)	$t_{1/2\beta}$ (h)	MRT (h)	AUC_{inf} (μg/ml · h)	Vss (l)	Clearances (l/h)			Percentage of dose in urine	
							Cl_{Tb}	Cl_r	Cl_{nr}	0–48 h	0–96 h
4	32	25	4.5[b]	10.2	144	21.4	2.09	1.12	0.97	51	54
2	32	25	6.7[c]	18.5	198	35.4	1.92	0.69	1.23	34	36
9	48	24	3.2	4.3	86.0	17.6	4.07	2.32	1.75	54	57
10	55	36	3.0	3.9	98.6	16.3	4.19	2.55	1.64	59	61
11	57	20	3.0[d]	4.6	91.6	12.2	2.62	1.54	1.08	56	59
7	61	40[e]	2.8	3.3	128	15.3	4.67	–	–	[f]	–
1	75	69	3.0	4.8	184	17.3	3.62	2.83	0.79	76	78
5	78	65	5.2	4.2	152	20.3	4.79	3.58	1.21	73	75
8	90	34[e]	2.8	3.6	101	17.9	5.02	3.63	1.39	70	72
6	99	30	2.8	2.8	60.0	20.1	7.22	4.71	2.51	64	65
3	101	44	2.5	4.0	141	20.6	5.23	3.72	1.51	69	71

[a] All platinum concentrations were expressed as μg equiv carboplatin
[b] $t_{1/2\gamma}$ of 24 h (MRT = 14 h)
[c] $t_{1/2\gamma}$ of 41.5 h (MRT = 32 h)
[d] $t_{1/2\gamma}$ of 5.7 h (MRT = 5.5 h)
[e] t_{max} was 0.75 h, others 0.5 h
[f] 62% in 16 h, 16–24 h urine lost

last time point when carboplatin could be quantitated. The mean ratios of the C_{max}, AUC_{inf}, and $AUMC_{inf}$ values for carboplatin/free platinum were essentially 1.0 over this time period. Significant concentrations of free, non-protein-bound platinum, representing metabolites or breakdown products, were not detected in the plasma. Therefore, following the administration of carboplatin, all of the free, non-protein-bound, ultrafilterable platinum is present as the parent compound.

In contrast to the pharmacokinetics of other anticancer drugs, carboplatin exhibited dose-independent or linear pharmacokinetics over a dose range of about 300–500 mg/m^2. Our results are in agreement with those of Harland et al. [9], who have reported that C_{max} values for ultrafilterable platinum and AUC_{inf} values for total platinum increased linearly with the dose over a range of 20–500 mg/m^2. They also extend to higher doses, the conclusion previously reported by Van Echo et al. [16] that the AUC_{inf} values for plasma, free platinum were linear with the dose over the range of 11–99 mg/m^2. The C_{max} values for carboplatin increased linearly with the dose in all 11 patients, whereas the AUC values increased linearly with the dose in those patients with a Cl_{cr} of 60 ml/min or greater.

Calvert et al. [2] have recently suggested that an absolute dose of carboplatin in mg should be given, instead of correcting for the patient's surface area and giving the dose as mg/m^2. Our data also support the use of a mg dose. The correlations between the AUC_{inf} and the dose were better when the doses were expressed as mg rather than as mg/m^2. Thus, better control of the total amount of carboplatin in the plasma could be achieved if absolute doses in mg were infused.

The mean (± SD) $t_{½\beta}$ for plasma, free platinum (3.1 ± 0.8 h) was the same as the $t_{½\beta}$ for carboplatin (3.0 ± 0.5 h). The former value was shorter than the free platinum $t_{½\beta}$ of 6.0 h previously reported by Harland et al. [9] but greater than the 2.2 h half-life reported by Koeller et al. [10]. Other half-lives previously reported for free platinum are 2.8 h [4], 1.7 ± 3.9 h [16], and 1.8 and 2.8 h [17], based on plasma samples collected for only 3–6 h postinfusion.

The mean (± SD) total body clearances for free platinum (77 ± 21 ml/min) and for carboplatin (74 ± 14 ml/min) were also essentially the same. These values are lower than the free platinum clearances of 123 ml/min and 106 ± 31 ml/min previously reported by Harland et al. [9] and Curt et al. [4], respectively. Therefore, our results indicate that carboplatin is cleared more slowly from the plasma than has previously been reported.

Bound platinum, however, accounting for approximately 30% of the platinum dose, was cleared even more slowly ($t_{½} \approx 5$ days) than free platinum. This fraction is probably a mixture of compounds, primarily proteins containing sulfhydryl or amine groups, that react rapidly and essentially irreversibly with the mono- or diaquated diammine platinum (II) species formed from carboplatin by the loss of the 1,1 cyclobutane dicarboxylic acid. The displacement of the latter by water molecules would produce the same highly reactive diammine platinum (II) intermediates that are produced by the displacement of the chlorine groups from cisplatin and would result in platination of the same endogenous compounds. The only difference is that the reactive products are formed at a slower rate from carboplatin than from cisplatin. The estimated half-life of about 5 days for bound platinum is probably an underestimation. Platinum concentrations of 0.7–2.5 μg equiv carboplatin/ml were still present in the plasma of all patients at 96 h. In addition, 0.4–0.5 μg equiv carboplatin/ml were found in predose plasma samples of two patients who received carboplatin about 1 month before the study. Platinum from carboplatin therefore becomes bound to endogenous plasma components and is slowly eliminated, probably at a rate equal to the normal half-life of the endogenous compounds.

The percentage of the platinum recovered in 24-h urine (67 ± 4%) of patients with a Cl_{cr} of 60 ml/min or greater ($n = 6$) was in good agreement with previously reported values of 63%–73% ($n = 38$) by Calvert et al. [1] and 65% ± 1% ($n = 14$) by Harland et al. [9], but greater than the 54% ± 6% reported by Van Echo et al. [16]. In addition, we found that the same mean percentage of the dose (70% ± 4%) was excreted as the parent compound in 24-h urine. The mean ratio of carboplatin/platinum in 24-h urine was 1.0 for all of the patients, including those with a Cl_{cr} of < 60 ml/min. This is in contrast to the results of Harland et al. [9], who have reported that 32% of dose was excreted as carboplatin in 24-h urine. The lower recovery of carboplatin by these investigators was, as they suggest, the result of degradation subsequent to the collection of the urine. This was avoided in the present study by the storage of the voided urine in a refrigerator, freezing of the samples at the end of the collction interval, and analysis of the samples within 1 week of collection. Our results show that all of the platinum excreted in 24-h urine is present as carboplatin.

Harland et al. [9] have reported a correlation ($r = 0.61$) between the Cl_{Tb} of free platinum and the glomerular filtration rate (GFR), and Egorin et al. [5] have reported a correlation ($r = 0.82$) between the Cl_{Tb} of free platinum and the Cl_{cr}. In contrast, our results did not show a good correlation ($r < 0.75$) between the Cl_{Tb} of carboplatin and the Cl_{cr}. Harland et al. [9] have also found a linear relationship ($r = 0.72$) between the Cl_r of free platinum and the GFR, whereas Egorin et al. [5] have reported a linear relationship ($r = 0.86$) between the percentage of platinum excreted in the urine and the Cl_{cr}. In this study, we found a linear relationship ($r = 0.88$) between the Cl_r of carboplatin and the Cl_{cr}.

Egorin et al. [5] have reported a relationship between the AUC_{inf} values for ultrafilterable platinum and the percentage of change in the platelet count. We did not find a relationship between the AUC_{inf} values for carboplatin and the percentage of change in the platelet count or the number of platelets lost. However, for six patients who received chemo- or radiation therapy within 1 year of entering the study, there was a good correlation ($r = 0.92$, $P = 0.01$) between the number of platelets lost and the area under the first moment curve ($AUMC_{inf}$).

The doses given to our patients were based on the equations previously developed by Egorin et al. [5]. However, in 7 of the 11 patients the platelet count dropped below 100000, and in 3 patients it fell below 20000. The equations, therefore, did not accurately predict nonthrombocytopenic doses for our patient population.

In this study, carboplatin over a dose range of about 300–500 mg/m^2 exhibited linear, dose-independent pharmacokinetics in patients with normal or slightly reduced

kidney function. However, since the major route of elimination of carboplatin is excretion via the kidneys, further decreases in kidney function result in decreased urinary excretion, with corresponding increases in AUC_{inf} and MRT values. Dose reductions are therefore needed in patients with a Cl_{cr} of less than about 60 ml/min to maintain their AUC_{inf} values for carboplatin at the same level as those in patients with normal or slightly reduced renal function.

Although based on limited data, the relationship between the MRT values and the Cl_{cr}, when the latter is less than about 60 ml/min, provides a means for calculating the extent of dose reduction in patients with mild renal failure. Since Cl_{Tb} (dose/AUC_{inf}) is equal to Vss/MRT, the substitution of the relationship between the MRT and the Cl_{cr} [Eq. (8)] for MRT and rearrangement give the following relationship:

$$\text{Dose (mg)} = \frac{\text{Vss} \cdot \text{AUC}_{inf}}{(-0.147\ Cl_{cr} + 11.8)} \qquad (10)$$

The calculation of the dose, as a percentage of the dose that would normally be given to patients with a Cl_{cr} of 60 ml/min or greater, indicates that patients with a Cl_{cr} of 50, 40, and 30 ml/min should be given 67%, 50%, and 40% of that dose, respectively. These dose reductions are greater than those previously predicted by the equations of Egorin et al. [5] but should result in consistent AUC_{inf} values, assuming that Vss is constant. Of course the latter may not be true for patients with significant ascites. To maintain constant $AUMC_{inf}$ values instead of constant AUC_{inf} values, the predicted doses would be even less (45%, 25%, and 16%), since the $AUMC_{inf}$ values are proportional to the square of the MRT value. Additional studies will be needed to determine the validity of these proposed dose reductions.

Conclusions

Carboplatin exhibits linear, dose-independent pharmacokinetics over a dose range of about 300–500 mg/m^2 (435–740 mg) in patients with creatinine clearances of about 60 ml/min or greater. Significant quantities of free, non-protein-bound, platinum-containing molcules other than carboplatin are not present in the plasma. However, the platinum from carboplatin becomes essentially irreversibly bound to plasma proteins and is eliminated slowly ($t_{½} \approx 5$ days) relative to the parent compound ($t_{½\beta}$ = 3 h). The AUC_{inf} values for carboplatin correlate better with the dose in mg than in mg/m^2, indicating that better control of the amounts of carboplatin in the plasma could be achieved by dosing on a mg basis without correcting for body surface area. Metabolites or platinum-containing degradation products of carboplatin are not excreted in the urine. Since the major route of elimination for carboplatin is excretion via the kidneys, dose reductions are necessary to prevent significant increases in AUC_{inf} values when creatinine clearances fall below about 60 ml/min.

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