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The disposition of carboplatin in the beagle dog

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Summary. Carboplatin was administered i.v. to four groups of three male beagle dogs at doses of 3, 6, 12, and 24 mg/kg (60–580 mg/m^2). Plasma samples were obtained at appropriate times and protein-free plasma ultrafiltrates (PU) were generated with Amicon Centrifree micropartition systems. Urine was collected at 24-h intervals for 96 h. PU and urine samples were analyzed for carboplatin by HPLC and for total platinum by atomic absorption spectrophotometry. Carboplatin accounted for about 90% of the free platinum in plasma. The Cmax and AUC_{inf} values for carboplatin and for free platinum increased linearly with dose. The terminal elimination half-life and mean residence times for carboplatin and free platinum were each about 1 h. Total-body clearances for carboplatin (5.6 l/h per m^2) and free platinum (5.1 l/h per m^2) were constant over the dose range studied, as were the respective volumes of distribution (5.7 and 5.0 l/m^2). A mean of 46% of the dose was excreted as carboplatin in 24-h urine; and by 72 h, 70% of the platinum administered was excreted in the urine. Free platinum was cleared by both renal and nonrenal processes. These results show that a dose of carboplatin is rapidly excreted in the urine and that carboplatin and plasma-free platinum exhibit linear pharmacokinetics in the beagle dog.

Introduction

Carboplatin, *cis*-diammine [1,1 cyclobutane dicarboxylato(2-)-0,0'] platinum II (CBDCA, JM-8, NSC241240, Paraplatin), is a second-generation platinum, containing antitumor agent (Fig. 1). It was selected for clinical evaluation based on its antitumor and toxicologic profiles in laboratory animals, which demonstrated that it was less nephrotoxic and less emetic than cisplatin (Platinol). These preclinical activities were reviewed recently by Rose and Schurig [7] and by Harrap [4]. The compound is presently undergoing phase II and phase III trials in the United States and Europe. Its primary advantage over cisplatin is that it does not cause serious renal toxicity; in addition it produces less severe nausea and vomiting and can be administered without added hydration. Phase I clinical data were recently reviewed by Calvert et al. [2]. To support the national and international registration of carboplatin and the interpretation of the toxicologic studies, we have determined the pharmacokinetics of parent compound and free and total platinum in the beagle dog following i.v. administration of carboplatin.

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Materials and methods

Animals. Twelve adult male, beagle dogs ranging in weight from 8.6 to 14.8 kg were randomly divided into four groups of three dogs. Prior to the start of the study, clinicopathological tests and physical examinations were performed to verify the health of the animals. Two days before each dose session, four dogs were placed in individual cages to acclimate them to the individual stainless steel cages equipped with urine collection pans. Water was supplied ad libitum, and food was provided once daily throughout the study.

Drug formulation. Vials of a clinical lot of carboplatin (Bristol-Myers Co., Syracuse, NY) containing 150 mg each of carboplatin and mannitol were diluted on the day of use with 5% dextrose (Travenol Labs. Inc., Deerfield, Ill) to give final nominal concentrations of 1.5, 3.0, 6.0, or 12.0 mg/ml.

Drug administration. A dose volume of 2 ml/kg was administered i.v. over 5 min via an indwelling catheter in a cubital vein. Four dogs were administered the drug during each of three study sessions. The first three dogs were given a dose of 24 mg/kg, the next three 12 mg/kg, and the subsequent groups of three dogs were given 6 mg/kg and 3 mg/kg, respectively. The total dose volume ranged from 17 to 30 ml per dog. Each of the dosing solutions was analyzed for carboplatin content within 48 h of preparation, and this concentration was multiplied by the total volume infused to give the total dose of carboplatin administered in milligrams.

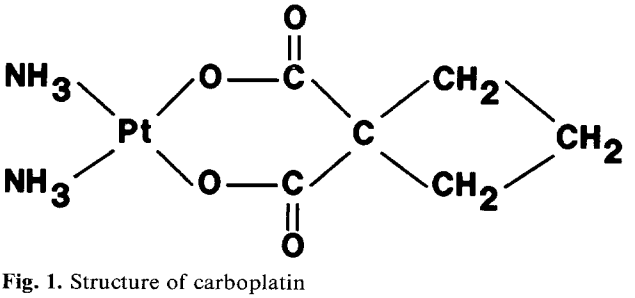

Fig. 1. Structure of carboplatin

Sample collection and processing. Blood samples (8 ml) were obtained by jugular venipuncture prior to drug administration and at the following times after administration: end of infusion (5 min), 12, 18, 30, and 45 min, 1, 1.5, 2, 3, 4, 6, 8, 24, and 72 h. The blood was collected in a labeled 10 ml Vacutainer tube containing sodium EDTA (Becton-Dickinson, no. 6457, Oxnard, Calif) and inverted gently to assure mixing. It was then centrifuged at 1000 *g* for 10 min at 5° C, and the plasma layer was removed immediately to a separate labeled, screw-capped tube.

Quadruplicate 0.5-ml samples of plasma were placed in individual Amicon Centrifree micropartition units (Amicon Corp. Danvers, Mass) and centrifuged at 200 *g* for 20 min to generate 100–200 µl plasma ultrafiltrate (PU). The PU was immediately transferred to labeled tubes, placed in dry ice, and stored at −60° C until analyzed. Quality control samples of carboplatin in control dog PU (0.5, 5.0, and 50 µg/ml) were prepared during each dosing session and were stored and analyzed along with the study samples.

Total urine output from each dog was collected for the intervals 0–24, 24–48, 48–72, and 72–96 h. The urine was collected in a container in dry ice to freeze the urine as quickly as possible after collection. The urine collection pans were rinsed with water after each collection interval and the rinses combined with the urines. The urine plus rinses were thawed, and the volume measured and recorded. The urines collected from the high-dose dogs from 0 to 24 h were diluted to 1000 ml. Other urines were diluted to 500 ml or left undiluted. Quadruplicate samples (2 ml) were transferred to labeled tubes, and immediately stored at −60° C until analyzed. Three quality control samples of carboplatin in control dog urine (10, 100, and 200 µg/ml) were prepared during each dosing session and were analyzed along with the study samples.

Analysis of carboplatin in plasma ultrafiltrate. Carboplatin concentrations in PU were quantitated by HPLC with a µBondapak NH_2 column, 10 µm, 3.9 × 300 mm (Waters Associates, Milford, Mass) and a mobile phase of CH_3CN/MeOH/0.005 *M* sodium perchlorate (pH 2.4) (75:15:10, v/v). The flow rate was 1.5 ml/min and detection was at 229 nm. Seven standards (0.2–20 µg/ml) in duplicate, quality control samples (0.5, 5.0, and 50 µg/ml) and samples (100 µl), appropriately diluted with control PU, were placed in 10 × 75 mm culture tubes. To each tube was added 50 µl of a 20 µg/ml solution of the internal standard, JM-10, [diammine(2-ethylmalonato)platinum II]. After mixing, the contents of the tubes were evaporated to dryness at 30° C under a stream of nitrogen. The residues were reconstituted with 0.1 ml MeOH/H_2O (9:1, v/v) and mixed for 30 s. The contents of the tubes were transferred to WISP vials containing limited volume inserts and were placed randomly in a WISP automatic injector (Waters Associates, Milford, Mass). Carboplatin and the internal standard eluted at 9.5–11 and at 11–13 min, respectively. Possible degradation products, cyclobutane mono- and dicarboxylic acids, eluted within 4 min. The peak height ratio (carboplatin/internal standard) versus carboplatin concentration was linear over a range of 0.20–20 µg carboplatin/ml PU.

The peak heights and peak height ratios of the reconstituted samples did not change after 48 h at room temperature. Based on the slope (1194) of a standard curve prepared in MeOH/H_2O and injected directly and the slope (1192) of a standard curve prepared as above, recovery was greater than 99%.

Correlation coefficients of each of six standard curves exceeded 0.990 and the mean (± SD) slope was 0.127 ± 0.003. At 0.5 µg/ml, the between- and within-day precision (%RSD) were 19% and 9%, respectively. At 5 and 50 µg/ml within-day precision (%RSD) was 3% or less and the between-day error was 5% or less. The mean recoveries for the quality control samples (n = 12) were 100%, 90%, and 91% of the nominal concentrations, respectively.

Analysis of carboplatin in urine. After a clean-up step on a column of activated carbon, the concentrations of carboplatin in urine were determined by HPLC with a Partisil PAC column, 10 µm, 4.6 × 250 mm (Whatman Separations, Inc., Clifton, NJ) and CH_3CN/H_2O (9:1, v/v) as the mobile phase. The flow rate was 2.0 ml/min, and detection was at 229 nm. Columns of activated carbon, SK4, 100/120 mesh (Alltech Associates, Deerfield, Ill) were prepared by adding two 1.0-ml samples of a 0.1 g/ml slurry in water to disposable filtration columns in a Baker-10 extraction system (J. T. Baker Co., Phillipsburg, NJ). After excess water had been removed by applying the vacuum for 30 s, the vacuum was turned off and 0.5 ml samples of standards (5 to 250 or 500 µg/ml in duplicate), quality controls (10, 100, 200 µg/ml), and study samples were added to the columns. After the urine had passed through the column, vacuum was reapplied and 0.5 ml of water was added. The vacuum was maintained for about 30 s to remove residual liquid. The columns were then transferred to 16 × 150 mm test tubes, and carboplatin was eluted by gravity flow with 10 ml MeOH. The effluents were evaporated to dryness under a stream of nitrogen and the residues were reconstituted in 0.5 ml water. The reconstituted sample was filtered through a Centrifree ultrafiltration unit (Amicon Corp. Danvers, Mass) by centrifugation at 200 *g* for 5 min, and the filtrate was transferred to a 300-µl microcentrifuge tube (Denville Scientific Inc., Denville, Mass). Standards, samples, and quality controls, were placed randomly in a WISP automatic injector (Waters Associates, Milford, Mass). Carboplatin eluted at 13–14 min.

Detector response (peak height) was linear from 5 to 500 µg carboplatin per ml urine. The correlation coefficient was greater than 0.990 and the mean (± SD) slope was 1.05 ± 0.06 (n = 5). Cyclobutane dicarboxylic acid did not elute within 45 min, and cyclobutane monocarboxylic acid eluted at 17.5–18 min. Based on a standard curve prepared in water and analyzed directly, the mean (± SD) recovery of carboplatin (n = 7) was 59% ± 4%. Within-day precision (%RSD) was 7%, 3%, and 3% at concentrations of 10, 100, and 200 µg/ml. The corresponding between-day error was 7%, 3%, and 12%. The mean recoveries of the nominal concentrations for these samples were 81% (n = 9); 95% (n = 6), and 103% (n = 4).

Analysis of total platinum in plasma ultrafiltrate and urine. Total platinum concentrations were determined by atomic absorption spectrophotometry with a Varian model AA 1475 instrument equipped with a model GTA-95 graphite tube atomizer (Varian Instruments, Sunnyvale, Calif). The current in the hollow cathode lamp was 9 mA, background correction was with a deuterium lamp, integration time

was 5 s, and the spectral band width was 0.2 nm at a monochromator wavelength of 265.9 nm. For PU, the furnace operating temperature was increased from 55° C to 1200° C in 6 steps over 100 s, held at 1200° C for 22 s for ashing, and then raised to 2650° C for 7.9 s for atomization. The flow rate of argon gas was 1.5–2.0 l/min. When required, samples were diluted with dog PU prior to analysis. At the start of each assay, a standard curve in PU was run consisting of five standards covering a range of 0.2–2.0 μg carboplatin eq/ml PU. The injection volume for standards and samples was 20 μl.

With sample dilution and multiple injections, valid results were obtained over a concentration range of about 0.1–220 μg carboplatin eq/ml PU. At concentrations of 0.5, 5, and 50 μg carboplatin eq/ml PU, within-day precision (%RSD) was 5% or less. The corresponding between-day precision was less than 6%. Mean recoveries were 98% (n = 13), 94% (n = 62), and 92% (n = 83) of the nominal concentrations, respectively.

For urine samples, the furnace temperature was increased from 65° C to 1200° C in 5 steps over 140 s, held at 1200° C for 26 s for ashing, and then raised to 2700° C for 4.9 s for atomization. The other operating parameters were the same as for PU, as were the concentrations of standards. With sample dilution and multiple injection, valid results were obtained for concentrations covering a range of 0.10–420 μg carboplatin eq/ml urine. At concentrations of 10, 100, and 400 carboplatin eq/ml, the within-day error (%RSD) was 6% or less. Between-day error was 3% or less. The mean recoveries were 99% (n = 30), 100% (n = 18), and 94% (n = 6) of the nominal concentration, respectively.

Data management and standard curves. The 1 V unattenuated output of the UV detector for the HPLC analysis of carboplatin in PU and urine was interfaced via an analog-to-digital converter to a Hewlett Packard model 3357 Laboratory Automation System (LAS) computer (Hewlett Packard, Palo Alto, Calif). The atomic absorption readings for total platinum in PU and urine were entered manually into the LAS system. The data was then transferred to a mainframe computer where Statistical Analysis System (SAS) software [8] calculated the standard curve parameters, the concentration values for samples and quality controls, and the pharmacokinetic and statistical parameters. Best-fit lines were estimated by the method of least squares and sample concentrations were obtained by inverse prediction [9]. Outliers in the standard curve were rejected by the method of Prescott [6]. If the predicted concentration of a sample was less than the concentration of the lowest standard, the value was reported as LLQ (lower than the limit of quantification). If the predicted concentration was 10% greater than the highest standard it was reported as greater than the limit of quantification, and the analysis was repeated on a diluted sample. The SAS procedure VARCOMP and the MINQUEO option calculated the within- and between-day variability for the quality control samples.

The standards data for PU concentrations of carboplatin was fitted by least-squares linear regression of concentration (weighted by 1/conc.) vs peak height ratio. The urine standards data of ln concentration carboplatin vs ln peak height was fitted similarly, but without a weighting factor.

The standards data for platinum in PU and urine (expressed as carboplatin equivalents) were fitted to a nonlinear curve of absorbance vs platinum concentration according to the following equation where A, B, and C are curve parameters:

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

Pharmacokinetic calculations. Plasma concentration (C) and time (t) data were analyzed by noncompartmental methods and moment analysis [3]. 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 of the post peak values. The data was fit to the function

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

starting with the last three non-zero data points. The last point at which C > LLQ was defined as time n. This procedure continued, adding preceding data points one at a time, until tmax was reached. The terminal log-linear portion was then defined by the data set yielding the largest correlation coefficient and was deemed to start at the earliest time point, point m, in the accepted data set. Half-life was then calculated from the slope (b) by

$$t_{1/2} = \ln 2/b \quad (3)$$

The areas under the C-vs-t curve (AUC) and the first moment of the C-vs-t curve (AUMC) were calculated to infinity using the trapezoidal rule. AUC and AUMC from zero time to time m (T_m) were calculated using the linear trapezoidal rule and from T_m to time n (T_n) in the log-linear portion were calculated using the log trapezoidal rule [9]. Mean residence time (MRT) was estimated by:

$$\text{MRT} = \text{AUMC}_{inf}/\text{AUC}_{inf} \quad (4)$$

Total-body clearance was calculated by dividing the carboplatin dose by the area under the plasma concentrations-vs-time curve from time 0 to infinity. Renal clearance was calculated by dividing the milligrams of carboplatin or platinum recovered in the 24-h urine by the area under the corresponding plasma concentration vs time curve.

The volume of distribution at steady state (V_{ss}) was calculated by the following equation where T is the infusion time [3]:

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

Results and discussion

The four analytical procedures employed in this study, namely the analysis of carboplatin in dog PU and urine by HPLC and the analysis of total platinum in the same matrices by atomic absorption (AA) spectrophotometry, were each developed and validated prior to analysis of the study samples. The validation procedures consisted in determining the linear range of the assay, the lower limit of quantitation, specificity, within- and between-day accuracy and precision, recovery and stability during the time required for analysis. In addition, quality control samples of carboplatin in dog PU and urine, covering the concentrations expected in these matrices, were prepared on the day of

Table 1. Identification, weight, and dose data for dogs administered carboplatin intravenously

Dog Number	Weight (kg)	SA[a] (m^2)	Dose of carboplatin	
			mg/kg	mg/m^2
1	11.8	0.518	24.4	556
2	13.9	0.578	24.2	581
3	10.8	0.489	24.4	540
4	12.2	0.530	11.6	267
5	14.8	0.603	12.2	299
6	11.1	0.498	11.9	265
7	12.5	0.539	6.0	139
8	13.7	0.572	5.9	142
9	14.0	0.581	6.0	145
10	8.6	0.420	3.0	61
11	10.3	0.473	3.1	67
12	11.0	0.495	3.0	67

[a] Surface Area (m^2) = 0.10 (weight in kg)$^{2/3}$

sample collection and were stored and analyzed along with the study samples. The results obtained with these quality control samples, (see Materials and methods) further verified the accuracy and reproducibility of each of the analytical methods employed in this study.

Three male beagle dogs each received 3, 6, 12, and 24 mg carboplatin per kg body weight as a 5-min infusion (Table 1). The mean plasma concentration-vs-time data for carboplatin and free platinum, expressed as microgram equivalents of carboplatin, obtained after each of the doses are given in Figs. 2 and 3, respectively. The tmax values for carboplatin and for free, non-protein-bound platinum corresponded to the end of the infusion (Table 2). The Cmax values for both species ranged from 16 to 20 µg or µg eq/ml plasma after the low dose of 3 mg/kg and increased linearly with dose ($r > 0.99$) to 145–175 µg/ml after the 24 mg/kg dose. The mean (± SD) ratio of (carboplatin Cmax)/(free platinum Cmax), calculated for individual dogs, was 0.92 ± 0.09 with a range of 0.82–1.07. Therefore, greater than 90% of the free, non-protein-bound platinum in the plasma at the end of the infusion was carboplatin.

The areas under the plasma concentration-vs-time curves for carboplatin and for free platinum (Table 2) also increased linearly with the dose in milligrams per square meter of body surface area ($r > 0.99$). The slope for carboplatin AUC_{inf}-vs-dose curve was 0.188, while the slope for free platinum AUC_{inf}-vs-dose was 0.224. The mean (± SD) ratio of (carboplatin AUC_{inf})/(free platinum AUC_{inf}), calculated for individual dogs, was 0.91 ± 0.08 with a range of 0.82–1.10. Therefore, at least 90% of the total free platinum in plasma was present as carboplatin. The mean (± SD) terminal elimination half-life for carboplatin for all dogs was 1.0 ± 0.3 h. The latter, as well as the mean residence time (1.1 ± 0.1 h), or the time required to eliminate 63.2% of the dose, was independent of dose. The mean (± SD) elimination half-life for total free platinum (0.9 ± 0.2 h) and its mean residence time (1.0 ± 0.1 h) in all dogs were the same as those for carboplatin. These results are the same as the t½β of 59 min reported for free platinum in a single dog after a dose of 12 mg/kg [10].

The overall mean (± SD) total-body clearances for carboplatin and for free platinum were 5.6 ± 0.5 and 5.1 ± 0.5 l/h per m^2, respectively. Both clearances were independent of dose over the range of 3–24 mg/kg (61–581 mg/m^2). The mean (± SD) ratio of (carboplatin clearance)/(free platinum clearance) for individual dogs was 1.11 ± 0.10 with a range of 0.91–1.21. These results show that parent compound was cleared at essentially the same rate as free platinum. The estimated mean volume of distribution for carboplatin at steady state (V_{ss}) was 5.7 ± 0.4 l/m^2 or 2.9 ± 0.3 l, while the V_{ss} for free platinum was 5.0 ± 0.4 l/m^2 or 2.6 ± 0.3 l. The V_{ss} values for both species were independent of dose.

Plasma concentrations of protein-bound platinum were determined by subtracting the PU platinum concentrations (free platinum) from the plasma concentrations of total platinum. Peak concentration of bound platinum oc-

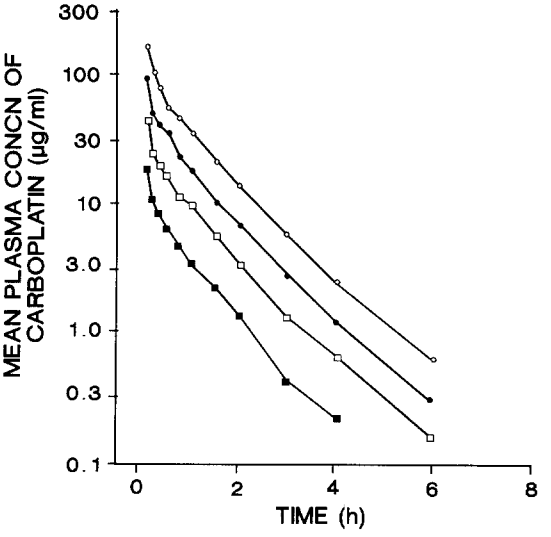

Fig. 2. Mean concentrations of carboplatin in dog plasma ultrafiltrate ($n = 3$) as a function of time after administration of 3 (■), 6 (□), 12 (●), and 24 (○) mg carboplatin/kg

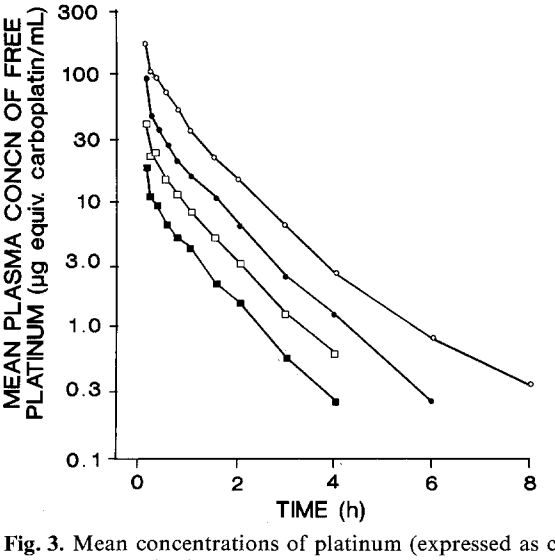

Fig. 3. Mean concentrations of platinum (expressed as carboplatin equivalents) in dog plasma ultrafiltrate ($n = 3$) as a function of time after administration of 3 (■), 6 (□), 12 (●), and 24 (○) mg carboplatin/kg

Table 2. Mean (±SD) pharmacokinetic values for carboplatin and plasma, free platinum (μg eq carboplatin) in beagle dogs ($n = 3$) after intravenous administration of carboplatin

Dose (mg/kg)	C_{max} (μg/ml)	AUC (μg·h·ml^{-1})	$t_{1/2}$ (h)	MRT (h)	Total body clearance (l/h/kg)	Total body clearance (l/h/m^2)	Renal clearance (l/h/m^2)	V_{ss} (l)	V_{ss} (l/m^2)	% of dose in urine 0–24 h	% of dose in urine 0–96 h
Carboplatin											
3	18±2	11±2	0.8±0.1	1.0±0.1	0.29±0.05	6.1±0.7	–	2.6±0.1	5.7±0.6	45±11	–
6	41±6	26±0	1.0±0.2	1.1±0.1	0.23±0.00	5.4±0.1	–	3.3±0.0	5.9±0.2	56± 7	–
12	83±7	51±5	1.2±0.4	1.1±0.1	0.23±0.02	5.4±0.2	–	3.1±0.3	5.7±0.4	37±15	–
24	149±8	104±5	1.0±0.2	1.1±0.1	0.23±0.01	5.4±0.4	–	2.9±0.3	5.5±0.1	48±13	–
Mean±SD ($n = 12$)	–	–	1.0±0.2	1.1±0.1	0.25±0.03	5.6±0.5	–	3.0±0.3	5.7±0.4	46±12	–
Free platinum (μg eq carboplatin)											
3	18±1	12±1	0.7±0.1	1.0±0.1	0.25±0.03	5.4±0.3	3.9±0.9	2.3±0.2	5.0±0.3	72±12	74±12
6	45±12	28±4	0.9±0.1	1.0±0.1	0.22±0.03	5.2±0.7	3.9±0.6	2.7±0.2	4.8±0.6	76± 5	78± 5
12	93±14	53±4	0.9±0.1	1.0±0.0	0.22±0.01	5.2±0.3	3.0±0.2	2.8±0.5	5.1±0.4	58± 8	61± 9
24	175±1	123±6	1.2±0.2	1.1±0.1	0.20±0.01	4.6±0.3	2.7±0.3	2.5±0.3	4.8±0.1	60±10	67± 6
Mean±SD ($n = 12$)	–	–	0.9±0.2	1.0±0.1	0.22±0.03	5.1±0.5	3.4±0.8	2.6±0.3	5.0±0.4	66±11	70±10

curred at 4–6 h and were 0.9–1.8 μg eq carboplatin/ml plasma in the dogs given 24 mg/kg. In the dogs given 3 mg/kg, peak concentrations of 0.2–0.5 μg eq/ml were seen at 4 h. Bound platinum concentrations were less than 0.1 μg eq/ml by 24 h in the dogs administered 6 mg/kg, but 0.6, 0.7, and 0.8 μg equiv/ml were still present at 72 h in the dogs given 24 mg/kg. The estimated terminal elimination half-life for bound platinum, calculated from the mean values at 8, 24, 48, and 72 h after the 24 mg/kg dose ($r = -0.99$), was 63 h.

Over the dose range of 3–24 mg/kg, an overall mean (± SD) of 70%±10% of the dosed platinum ($n = 12$) was excreted in 96 h (range 51%–85%) with most of this occurring within the first 24 h (Table 2). From 48 to 72 h, only 1% or less of the platinum dose was excreted in the urine. These recoveries are less than the 95% recovery in 7 days found after administration of 12 mg/kg to a single dog [10]. However, they are comparable to the urinary recoveries of platinum (60%–70%) found 4 h after administration of cisplatin (1 mg/kg) to adult female beagle dogs [5] and to the 67% (range 63–73%) seen in humans following 1 h infusions of 20–520 mg carboplatin/m^2 [1]. The mean (± SD) renal clearance for free, ultrafilterable platinum was 3.4±0.8 l/h per m^2, compared with a total-body clearance of 5.1±0.5 l/h per m^2. Therefore, free, ultrafilterable platinum was also cleared by non-renal processes. Excretion via the kidneys, however, is the major route of elimination for platinum from a dose of carboplatin in both dogs and humans.

Carboplatin was rapidly excreted and in most cases accounted for 60% or more of the total platinum in 24-h urine. An overall mean (±SD) of 46±12% of the carboplatin dose ($n = 12$) was excreted in 24 h as carboplatin (range 21–63%). With the exception of one high-dose dog, carboplatin was not detected in urine collected over the 24–48 h interval. The ratio of carboplatin/platinum in the 0–24 h urine ranged from 0.6–0.9 in 10 of the 12 dogs with ratios of 0.3 and 0.4 for dogs 6 (12 mg/kg) and 10 (3 mg/kg), respectively. The variability in the ratio of carboplatin/platinum in the urine may be a reflection of the variable retention time in the bladder, since preliminary data from this laboratory indicate that carboplatin is unstable in dog urine in vitro (38° C).

Side-effects and toxicity were seen after the higher doses of carboplatin. All of the dogs that received 24 mg/kg vomited within 7 h of drug administration and 2 of the 3 dogs that received 12 mg/kg vomited between 7 and 24 h afterwards. The physical condition of the dogs that received 24 mg/kg deteriorated to such an extent that they were euthanized 13–15 days after administration. A necropsy revealed multiple hemorrhages, probably due to thrombocytopenia. The dogs that received the lower doses did not develop any overt signs of toxicity.

Conclusions

The results of this study demonstrate that carboplatin exhibits linear, dose-independent pharmacokinetics in the beagle dog at doses comparable to those administered to humans. Cmax and AUC_{inf} values increased linearly with dose, while plasma half-life, mean residence time, volume of distribution, and total body clearances for carboplatin were constant across doses. No significant quantities of free, platinum-containing metabolites were detected in plasma, and as in humans the major route of elimination was excretion via the kidneys.

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