Cancer Chemother Pharmacol (1988) 21: 19–24

Cancer Chemotherapy and Pharmacology

Comparative distribution and excretion of carboplatin and cisplatin in mice

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Summary. The comparative distribution and excretion of Carboplatin (*cis*-diammine-1,1-cyclobutane dicarboxylate platinum II, CBDCA, JM8) and cisplatin have been investigated in Balb C$^-$ mice following i.v. administration of the maximally tolerated doses (MTDs) of the compounds. Although the concentrations of platinum in the plasma and tissues during the α-phase were much higher for Carboplatin than for cisplatin, reflecting the difference in the doses used (4 vs 80 mg/kg), the tissue-to-plasma ratios were similar. During the β-phase (1–10 days), however, both the platinum concentrations and the ratios were found to be similar for most tissues when cisplatin and Carboplatin were compared. The platinum concentrations and the tissue-to-plasma ratios of the spleen, brain, muscle, testes, ovary and bile, on the other hand, were consistently higher (two- to sixfold) after Carboplatin than after cisplatin. The highest ratios (>20) were found in the kidney, liver, spleen (after Carboplatin only) and skin at 6 days after treatment. Comparison of the two compounds showed that the half-lives of platinum in the plasma and tissues during both the α- and β-phases were similar, except for the spleen, in which a nine-fold greater $t^{1}/_{2\beta}$ was recorded for Carboplatin than for cisplatin. The main route of excretion for the two complexes is via the kidneys, with 52% of cisplatin and 93% of Carboplatin being excreted during the first 3 days. The major part of this, however, is excreted within the 1st day. These results indicate that, although there are quantitative differences, the distribution and excretion profiles are similar for Carboplatin and cisplatin.

Introduction

Since its introduction into clinical practice, cisplatin has shown activity against several human neoplasms, particularly those of the ovary, the testes, and the head and neck [16]. However, this compound produces several dose-limiting toxicities, notably nausea and vomiting, ototoxicity, myelotoxicity, peripheral neuropathy and, in particular, nephrotoxicity [16]. A second generation analogue, Carboplatin (*cis*-diammine-1,1-cyclobutane dicarboxylate platinum II, CBDCA, JM8) (Fig. 1), has been identified by our Department as a viable alternative to cisplatin in cancer chemotherapy [5]. The analogue not only displays a broad spectrum of antitumour activity, but is also devoid of nephrotoxic activity in rodents in contrast to the parent compound.

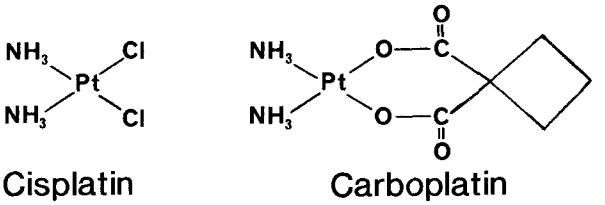

Fig. 1. Structures of cisplatin and carboplatin

As part of the pharmacological evaluations of Carboplatin, we have studied its distribution and excretion in mice following i.v. administration. Parallel studies were conducted with cisplatin, mainly to determine whether the comparative distribution and excretion patterns of the two drugs would provide an explanation for the inability of Carboplatin to elicit nephrotoxicity.

Materials and methods

Chemicals. Carboplatin and cisplatin were gifts from the Johnson Matthey Research Centre (Sonning Common, Reading, England). The compounds were dissolved in normal saline immdiately prior to administration.

Tissue distribution studies. Male and female Balb C$^-$ mice (20–25 g) bred at The Institute of Cancer Research were used throughout. Animals received maximally tolerated doses of cisplatin (4 mg/kg) or Carboplatin (80 mg/kg) via the tail vein (10 ml/kg), and were killed serially (3 per time point) by cervical dislocation. Blood was collected immediately from the axillary vessels in heparinized tubes and centrifuged in a Beckman Microfuge (model B) to obtain the plasma. Whole organs or representative tissue samples were removed and weighed where necessary. Bile was collected from the gallbladder. Bone marrow was prepared by washing out each femur with 1 ml saline. Plasma, bile and tissues were stored at −20° C prior to analyses.

Urinary excretion studies. Separate groups of animals received i.v. injections of the compounds as above and were placed in metabolism cages. Urine was collected daily for 3 days and stored frozen until analysed.

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Plasma binding studies. Plasma was obtained from male Balb C$^-$ mice. Cisplatin (5 μg/ml final concentration) and Carboplatin (50 μg/ml final concentration) were added to separate plasma pools and incubated at 37° C. Free platinum in the plasma was determined following ultrafiltration at 4° C using Amicon CF50A membrane cones as described by Litterst et al. [13]. The combined free and reversibly bound platinum was determined in the soluble fraction following the addition of an equal volume of cold trichloroacetic acid (20%, w/v) to a separate aliquot of the incubation mixture.

Tissue analysis. Samples were analysed for their platinum content using a Perkin Elmer Flameless Atomic Absorption Spectrophotometer (model 306) as described by Leroy et al. [10]. Plasma, plasma ultrafiltrate, plasma-trichloroacetic acid supernatant, urine and bile samples were analysed directly. Tissue samples (up to 200 mg), however, required prior digestion in nitric acid (sp. gr. 1.4; 2 ml). Gentle heating was required to complete the digestion. Following evaporation to near dryness, the digests were taken up in 1 *N* HCl (2 ml) and again heated to near dryness to remove excess nitric acid. After repeating this last stage with 0.1 *N* HCl (2 ml), the digests were finally dissolved in 1 ml 0.1 *N* HCl for platinum analysis. The method permits estimation of total platinum metal in biological samples and no attempt was made to identify the nature of the metal ion present. Protein content of the bone marrow was determined by the Lowry procedure [14].

Pharmacokinetic analysis. The plasma or tissue concentration-time data for platinum were fitted to a two-compartment open model using a non-linear least-squares computer program [7] with $1/(C + \hat{C})^2$ as the weighting function [15]. A one-compartment open model was used to fit the plasma binding-time data in a similar way.

Results

At maximally tolerated doses, neither Carboplatin nor cisplatin has any effect on body weight or heart, liver, lung and kidney weights (Table 1). However, both compounds elicit a decrease in spleen weights, which recover subsequently. In the case of cisplatin, this is followed by a period of hyperplasia.

The comparative tissue distributions of Carboplatin and cisplatin are shown in Tables 2 and 3. The initially greater concentrations of platinum after Carboplatin than after cisplatin are due to the larger dose of Carboplatin used. However, during days 1–10, the platinum concentrations in the plasma and most of the tissues were similar for cisplatin and Carboplatin. The spleen, brain, muscle, testes, ovary and bile, on the other hand, consistently show a 2- to 6-fold greater concentration of platinum after Carboplatin throughout this time. There was no sex difference in the tissue distribution of the two platinum complexes (data not shown).

Platinum from Carboplatin or cisplatin persists in the tissues for at least 10 days. This, coupled to the relatively lower half-life of platinum in the plasma, results in the progressive increase in the tissue-to-plasma ratios with time for most of the tissues examined (see Table 4). Table 4 indicates that the ratios for Carboplatin and cisplatin are similar during the initial decay phase and, for most tissues, also during the terminal phase. Again, in the spleen, brain, muscle, testes, ovary and bile there were consistently higher tissue-to-plasma ratios after Carboplatin than after cisplatin during the latter phase. The high bile-to-plasma ratio may not be indicative of the presence of an active biliary transport process for platinum since gallbladder bile, and not canalicular bile, was assayed. At 6 days after treatment with Carboplatin and cisplatin, the kidney, liver, spleen (after Carboplatin only) and skin had both the

Table 1. Body and organ weights following carboplatin and cisplatin administration

	Weights[a]				
	10 min	1 day	2 days	6 days	10 days
Body weight					
CarboPt	26.7 ±0.6[b]	26.0 ±1.0	25.0 ±0.6	26.0 ±0.6	26.1 ±1.0
CisPt	25.3 ±0.6	23.7 ±1.2	26.0 ±1.0	23.0 ±0.5	26.7 ±0.6
Heart					
CarboPt	0.47±0.04	0.42±0.01	0.45±0.02	0.47±0.04	0.45±0.04
CisPt	0.50±0.03	0.44±0.03	0.42±0.01	0.46±0.02	0.46±0.02
Liver					
CarboPt	4.76±0.55	4.59±0.03	5.14±0.28	4.89±0.41	5.42±0.19
CisPt	5.67±0.26	4.77±0.17	4.79±0.23	4.74±0.32	5.40±0.25
Lung					
CarboPt	0.61±0.02	0.53±0.05	0.56±0.07	0.56±0.05	0.57±0.05
CisPt	0.61±0.03	0.56±0.03	0.56±0.02	0.68±0.08	0.63±0.12
Kidney					
CarboPt	1.69±0.15	1.53±0.01	1.65±0.20	1.53±0.13	1.70±0.13
CisPt	1.77±0.19	1.62±0.15	1.56±0.05	1.57±0.08	1.64±0.07
Spleen					
CarboPt	0.47±0.04	0.39±0.06	0.34±0.03	0.34±0.07	0.50±0.11
CisPt	0.48±0.10	0.42±0.11	0.30±0.03	0.62±0.21	0.80±0.34

[a] Values shown are in grams for the body weight, and grams per 100 grams of body weight for the organs
[b] Mean ± SD; $N = 3$

Table 2. Tissue distribution of carboplatin and cisplatin in male mice

Tissue		Platinum concentration[a]						
		10 min	60 min	4 h	1 day	2 days	6 days	10 days
Plasma	CarboPt	57.6	19.3	1.6	0.45	0.19	0.07	N.D.
	CisPt	4.7	0.94	0.62	0.31	0.18	0.04	N.D.
Kidney	CarboPt	154.7	40.2	7.0	4.8	2.8	2.1	0.96
	CisPt	7.3	5.2	4.0	3.4	2.0	1.2	0.87
Liver	CarboPt	47.9	42.1	5.6	5.1	4.0	3.1	1.6
	CisPt	4.7	4.9	3.5	3.6	2.8	2.6	1.0
Lung	CarboPt	33.8	14.7	3.4	1.7	1.4	0.90	0.52
	CisPt	1.9	1.3	1.1	0.98	0.74	0.43	0.32
Heart	CarboPt	14.1	4.7	0.97	0.62	0.55	0.46	0.31
	CisPt	0.90	0.48	0.41	0.39	0.31	0.27	0.23
Ileum	CarboPt	26.5	22.3	9.2	4.5	2.1	0.58	0.34
	CisPt	4.2	3.4	2.4	1.2	0.98	0.32	0.23
Spleen	CarboPt	16.7	11.0	2.7	2.1	2.6	2.6	2.2
	CisPt	1.2	1.0	0.81	0.78	0.89	0.62	0.40
Brain	CarboPt	2.0	0.83	0.24	0.32	0.20	0.17	0.12
	CisPt	0.079	0.058	0.038	0.042	0.040	0.033	0.056
Muscle	CarboPt	10.2	3.7	1.2	1.5	0.78	0.57	0.39
	CisPt	0.57	0.31	0.32	0.28	0.18	0.22	0.17
Skin	CarboPt	49.3	19.8	7.2	5.4	3.9	2.8	2.6
	CisPt	4.1	2.6	2.2	1.7	1.8	1.8	1.2
Fat	CarboPt	4.5	1.9	0.28	0.15	0.05	0.03	0.05
	CisPt	0.17	0.01	0.04	0.04	0.03	0.04	0.03
Testes	CarboPt	6.1	2.4	0.81	0.48	0.33	0.33	0.26
	CisPt	0.40	0.18	0.17	0.19	0.10	0.10	0.09
Bone marrow	CarboPt	0.160	0.102	0.039	0.023	0.009	0.011	0.008
	CisPt	0.012	0.012	0.008	0.010	0.009	0.007	0.008
Bile	CarboPt	22.1	28.4	23.3	3.4	2.0	0.40	0.36
	CisPt	3.4	4.6	7.5	0.48	0.42	0.06	N.D.

[a] The mean ($N = 3$) platinum concentrations are expressed in micrograms per millilitre for plasma and bile, micrograms per milligram of protein for bone marrow, and micrograms per gram of wet weight for the tissues. Standard deviations were less than 20% of the means
N.D., not detectable

Table 3. Tissue distribution of carboplatin and cisplatin in female mice

Tissue		Platinum concentration[a]						
		10 min	60 min	4 h	1 day	2 days	6 days	10 days
Plasma	CarboPt	76.1	14.3	0.79	0.36	0.23	0.13	0.03
	CisPt	5.9	0.59	0.38	0.30	0.16	0.04	N.D.
Ovary	CarboPt	49.1	13.9	3.4	3.6	3.1	1.4	2.9
	CisPt	2.3	1.4	0.77	0.53	0.53	N.D.	N.D.
Uterus	CarboPt	52.9	25.1	4.8	2.5	3.2	1.1	1.1
	CisPt	3.3	1.2	1.0	1.2	0.58	0.78	0.43

[a] The mean ($N = 3$) platinum concentrations are expressed in micrograms per millilitre for plasma and micrograms per gram of wet weight for the tissues. Standard deviations were less than 20% of the means
N.D., not detectable

highest platinum concentrations (1–3 μg/g) and the highest tissue-to-plasma ratios (>20).

The plasma and tissue platinum concentrations-time data were fitted, where possible, to a two-compartment open model, and the results are shown in Table 5. The tissue half-lives of platinum after Carboplatin and cisplatin are not grossly dissimilar, except in the spleen, where the β-phase half-life is 9-fold greater for Carboplatin (1507 h) than for cisplatin (173 h). This result is partly due to the differential effect of the two compounds on the spleen wet weight (Table 1). The enlarged spleen after cisplatin results in an apparently lower platinum concentration during days 6 and 10, and this becomes translated into a lower β-phase half-life than would otherwise be expected for this compound.

The binding of platinum to plasma protein is shown in Fig. 2, and the results of the computer fit of the data are shown in Table 6. Only the data obtained within the first

Table 4. Tissue to plasma ratios of platinum following carboplatin and cisplatin administration to mice

Tissue		Tissue to plasma ratios[a]					
		10 min	60 min	4 h	1 day	2 days	6 days
Kidney	CarboPt	2.7	2.1	4.4	10.7	15.1	28.4
	CisPt	1.6	5.5	6.3	11.1	11.2	34.5
Liver	CarboPt	0.83	2.2	3.5	11.3	21.5	43.0
	CisPt	1.0	5.2	5.5	11.8	16.3	73.2
Lung	CarboPt	0.59	0.76	2.1	3.8	7.6	12.3
	CisPt	0.41	1.4	1.7	3.2	4.2	12.3
Heart	CarboPt	0.24	0.24	0.61	1.4	3.0	6.3
	CisPt	0.19	0.51	0.66	1.3	1.8	7.8
Ileum	CarboPt	0.46	1.2	5.8	10.1	11.3	7.9
	CisPt	0.89	3.6	3.9	4.0	5.6	9.0
Spleen	CarboPt	0.29	0.57	1.7	4.8	13.8	35.2
	CisPt	0.26	1.1	1.3	2.6	5.1	17.7
Brain	CarboPt	0.04	0.04	0.15	0.72	1.1	2.3
	CisPt	0.02	0.06	0.06	0.14	0.23	0.94
Muscle	CarboPt	0.18	0.19	0.72	3.3	4.2	7.8
	CisPt	0.12	0.33	0.51	0.90	1.1	6.3
Skin	CarboPt	0.86	1.0	4.5	12.1	21.1	38.5
	CisPt	0.89	2.8	3.5	5.6	10.2	50.3
Fat	CarboPt	0.08	0.10	0.18	0.34	0.27	0.42
	CisPt	0.04	0.11	0.07	0.14	0.17	1.3
Testes	CarboPt	0.11	0.12	0.50	1.1	1.8	4.5
	CisPt	0.09	0.19	0.27	0.61	0.58	2.7
Ovary	CarboPt	0.65	0.97	4.3	9.9	13.5	10.7
	CisPt	0.39	2.4	2.0	1.8	3.3	–
Uterus	CarboPt	0.70	1.8	6.1	6.9	13.6	8.7
	CisPt	0.55	2.0	2.6	4.1	3.6	19.6
Bile	CarboPt	0.38	1.5	14.6	7.6	10.5	5.7
	CisPt	0.72	4.9	12.1	1.5	2.3	1.5

[a] The values were derived from results presented in Tables 2 and 3

8 h following incubation of cisplatin with the plasma were used for the computer fit, since the results obtained after this time did not conform to a monoexponential decay. It is clear from Fig. 2 and Table 6 that irreversible binding of cisplatin to the plasma proteins is more rapid ($t_{1/2}$ = 3 h) than that of Carboplatin ($t_{1/2}$ = 44–46 h). The concentration of platinum from cisplatin in both the plasma ultrafiltrate and the supernatant following trichloroacetic acid addition to the plasma are alamost identical, indicating the absence of any reversible binding of cisplatin to plasma. In the case of Carboplatin, however, the platinum level in the ultrafiltrate is lower than that in the acid-soluble fraction by about 16%, which represents reversible binding of Carboplatin to plasma.

Urinary excretion of platinum after Carboplatin is similar for the two doses that were studied (Table 7). The 3-day cumulative Pt excretion after Carboplatin, however, is about two-fold greater than after cisplatin (93% vs 52%). With both compounds, the bulk of the excretion occurs during the 1st day, with only 1%–2% of the dose being eliminated during the next 2 days.

Discussion

The distribution and excretion of cisplatin have previously been studied in mice [6, 8], rats [4, 12, 18, 20], rabbits [7] and dogs [12, 17], and our results with this compound in mice are generally in agreement with the reported data. Furthermore, the results of our comparative study demonstrate that the distribution and excretion of Carboplatin are temporally similar to those of cisplatin. There are, however, substantial quantitative differences both in vitro and in vivo which distinguish Carboplatin from cisplatin. In vitro, irreversible binding of platinum to mouse plasma is more rapid with cisplatin than with Carboplatin. This finding is similar to that reported for rat [3] and human [19] plasmas. It is understood from kinetic measurements with cisplatin that the limiting step in either the general binding of platinum to macromolecules or the critical cytotoxic interaction with DNA is the rate of chemical conversion to the active platinum species [9]. Since this would almost certainly also apply to Carboplatin, the observed differences in the rate of irreversible binding of the two compounds is probably a function of the greater chemical stability and, therefore, lower rate of activation of the analogue as compared to the parent compound [2]. In vivo, the greater stability of Carboplatin is, however, compensated by the higher dose requirement. Irreversible binding probably accounts for the long β-phase half-lives in vivo for platinum in the plasma and tissues after both cisplatin and Carboplatin.

Table 5. Computer-derived constants and half-lives for carboplatin and cisplatin following a two-compartment pharmacokinetic analysis of concentration-time data

Tissue	Pharmacokinetic parameters[a]					
	A	α	$t_{1/2\alpha}$	B	β	$t_{1/2\beta}$
Plasma						
CarboPt	58.80± 8.5[b]	1.02±0.08	0.68	0.47±0.08	0.014 ±0.002	49.5
CisPt	6.02± 1.18	2.61±0.41	0.27	0.51±0.05	0.019 ±0.001	36.5
Kidney						
CarboPt	174.20±33.7	1.52±0.27	0.46	5.18±0.55	0.0073 ±0.0008	94.9
CisPt	4.00± 0.84	0.43±0.18	1.63	3.05±0.31	0.0058 ±0.0008	119
Liver						
CarboPt	60.00± 9.0	0.89±0.16	0.78	5.11±0.64	0.0047 ±0.0009	147
CisPt	1.15± 0.73	0.67±1.15	1.03	3.89±0.34	0.0052 ±0.0006	133
Lung						
CarboPt	34.80± 4.6	0.93±0.13	0.75	1.88±0.20	0.0055 ±0.0008	126
CisPt	1.05± 0.32	1.14±0.55	0.61	1.02±0.06	0.0054 ±0.0005	128
Heart						
CarboPt	13.80± 2.2	1.08±0.18	0.64	0.65±0.07	0.0030 ±0.0008	231
CisPt	0.73± 0.16	2.09±0.58	0.33	0.39±0.02	0.0025 ±0.0004	277
Ileum						
CarboPt	25.50± 5.1	0.39±0.11	1.78	3.71±0.66	0.0111 ±0.0013	62.4
CisPt	2.26± 0.48	0.18±0.11	3.85	1.28±0.19	0.0079 ±0.0010	87.7
Spleen						
CarboPt	17.70± 2.4	0.87±0.16	0.80	2.34±0.22	0.00046±0.00067	1507
CisPt	0.39± 0.31	1.43±2.29	0.48	0.93±0.09	0.0040 ±0.0008	173
Muscle						
CarboPt	11.80± 2.7	1.61±0.38	0.43	1.13±0.13	0.0046 ±0.0010	150
CisPt	0.42± 0.13	2.16±1.05	0.32	0.26±0.02	0.0019 ±0.0006	364
Skin						
CarboPt	41.60± 8.0	0.93±0.24	0.75	5.00±0.67	0.0031 ±0.0010	223
CisPt	2.73± 0.52	1.48±0.45	0.47	1.97±0.10	0.0017 ±0.0004	407

[a] Results are expressed in micrograms per millilitre or per gram for A and B and per hour for α and β, and in hours for $t_{1/2\alpha}$ and $t_{1/2\beta}$
[b] Mean ± SE

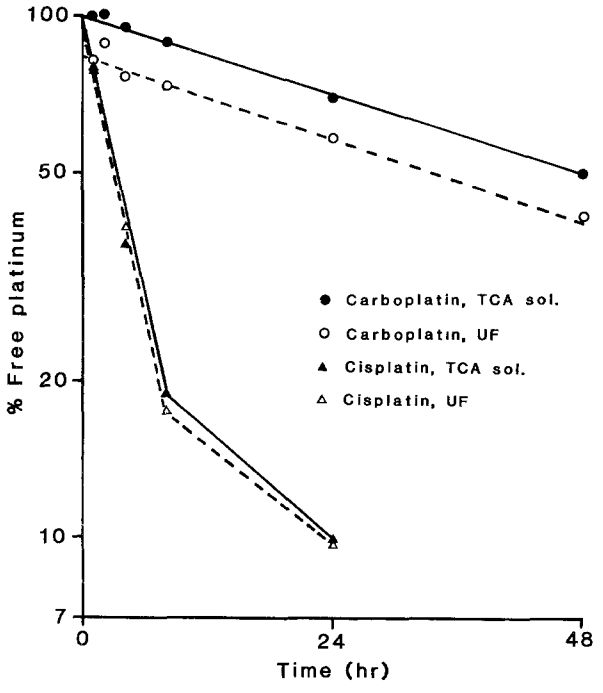

Table 6. A one-compartment pharmacokinetic analysis of the binding of carboplatin and cisplatin to mouse plasma

	A (%)	α (h^{-1})	$t_{1/2\alpha}$ (h)
Carboplatin			
Ultrafiltrable platinum	84.1±4.8[a]	0.015±0.002	45.8
TCA-soluble platinum	102.8±5.2	0.016±0.002	44.1
Cisplatin			
Ultrafiltrable platinum	99.5±3.9	0.22 ±0.01	3.2
TCA-soluble platinum	97.4±4.6	0.21 ±0.01	3.3

[a] Mean ± SD; $N = 3$

The difference in the in vivo results between Carboplatin and cisplatin relate to both the urinary excretion and tissue concentration of platinum. Excretion is predominantly via the renal route, elimination being about two-fold greater for Carboplatin than for cisplatin. This difference is probably due to the more rapid and extensive binding of the parent compound to macromolecules,

Fig. 2. Binding of carboplatin (50 μg/ml) and cisplatin (5 μg/ml to mouse plasma in vitro. Platinum in the ultrafiltrate (UF) represents free drug, whereas the TCA-soluble fraction represents combined free and reversibly bound material. Each *point* is a mean of three separate determinations

Table 7. Urinary excretion of platinum following carboplatin and cisplatin administration to male mice

Time (days)	Cumulative excretion (% dose)		
	Cisplatin 4 mg/kg	Carboplatin	
		5 mg/kg	80 mg/kg
1	50.3 ± 3.7[a]	90.8 ± 6.9	90.2 ± 1.2
2	51.2 ± 3.8	92.6 ± 6.4	91.5 ± 0.5
3	51.6 ± 3.6	92.8 ± 6.4	92.6 ± 0.3

[a] Mean ± SD; $N = 3$

thereby reducing the amount available for renal elimination. With biliary excretion being minimal, it can be calculated from the urinary excretion that the amount of platinum retained in vivo at 3 days is over two-fold greater for Carboplatin than for cisplatin (3.1 vs 1.3 mg/kg). This is in keeping with the observed higher concentrations of platinum during the β-phase in the spleen, brain, muscle, testes, ovary and bile following Carboplatin administration. In the remaining tissues and in the plasma, however, maximally tolerated doses of Carboplatin and cisplatin produce similar platinum levels during the terminal decay phase. Of particular interest is the similar platinum concentration in the kidney in spite of the toxicological significance of this organ with cisplatin in contrast to Carboplatin [5, 11]. This would suggest that the mechanism of, and the subcellular target sites for, the chemical-biological interactions in the kidney may be quite different for Carboplatin and cisplatin.

Differences between Carboplatin and cisplatin, both in urinary excretion and in plasma protein binding, may derive from differences in the chemical reactivities of the two compounds, the leaving groups of the parent drug being far more labile than in the analogue. However, such differences in reactivities cannot account for the greater concentration of platinum in some tissues after Carboplatin than after cisplatin administration. In these cases it may be that some tissue-selective activation of the Carboplatin molecule occurs.

In conclusion, maximally tolerated doses of Carboplatin and cisplatin produce similar tissue distribution and excretion profiles, although some quantitative differences between the two complexes are observed. These results, however, do not provide an explanation for the lack of renal toxicity of Carboplatin, compared with cisplatin.

Acknowledgements. The authors wish to thank Miss A. Robinson for typing the manuscript. This work was supported by grants from the Cancer Research Campaign/Medical Research Council, U. K.

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Received September 12, 1986/Accepted August 19, 1987