[CANCER RESEARCH 44, 1693–1697, April 1984]

Pharmacokinetics of *cis*-Diammine-1,1-cyclobutane Dicarboxylate Platinum(II) in Patients with Normal and Impaired Renal Function[1]

Stephen J. Harland, David R. Newell,[2] Zahid H. Siddik, Ruth Chadwick, A. Hilary Calvert, and Kenneth R. Harrap

Department of Biochemical Pharmacology, Institute of Cancer Research [D. R. N., Z. H. S., R. C., A. H. C., K. R. H.], and Division of Medicine, Royal Marsden Hospital and Institute of Cancer Research [S. J. H., A. H. C.], Sutton, Surrey, England

ABSTRACT

cis-Diammine-1,1-cyclobutane dicarboxylate platinum(II) (CBDCA, JM8) is a nonnephrotoxic analogue of cisplatin currently undergoing clinical evaluation. Pharmacokinetic studies have been performed in patients receiving CBDCA (20 to 520 mg/sq m) as a 1-hr infusion without hydration or diuresis. Following the end of the infusion, plasma levels of total platinum and ultrafilterable (M_r < 50,000) platinum (free platinum) decayed biphasically with first-order kinetics (total platinum $t^{\alpha}_{1/2}$ = 98 min; $t^{\beta}_{1/2}$ range, 399 to >1440 min; free platinum $t^{\alpha}_{1/2}$ = 87 min; $t^{\beta}_{1/2}$ = 354 min). During the first four hr, binding of platinum to plasma protein was limited (24%), with most of the free platinum in the form of unchanged CBDCA (94%). However, by 24 hr, the majority of platinum was protein bound (87%). The major route of elimination was renal, 65% of the platinum administered being excreted in the urine within 24 hr, with 32% of the dose excreted as unchanged CBDCA. No evidence was found from studies on the renal clearance of free platinum to indicate renal tubular secretion (mean free platinum renal clearance, 69 ml/min). However, the plasma clearance of free platinum did correlate positively with glomerular filtration rates (p = 0.005). None of the pharmacokinetic parameters determined were dose dependent. *In vitro* studies with plasma and urine demonstrated that, in contrast to cisplatin, CBDCA is a stable complex [$t_{1/2}$ - 37°; plasma, 30 hr, and urine (range), 20 to 460 hr]. The differences in the pharmacokinetics of cisplatin and CBDCA may explain why the latter complex is not nephrotoxic.

INTRODUCTION

Cisplatin [*cis*-diamminedichloroplatinum(II), Chart 1*A*] is a platinum coordination complex currently used widely in anticancer regimens. Cisplatin is active against testicular and ovarian neoplasms and has also been used with some success against tumors of the lung, bladder, cervix, and head and neck (22). Its toxicity is, however, considerable. Kidney damage and vomiting are serious problems and, in addition, hearing loss, peripheral neuropathy, and anemia are frequently seen (18, 22, 27). In an attempt to improve the clinical utility of platinum coordination complexes, a number of groups have sought a nonnephrotoxic cisplatin analogue with equivalent or superior antitumor activity (12). As a result of these studies, a number of complexes have recently undergone or are currently undergoing clinical evaluation (2, 4, 12, 17).

CBDCA[3] (Chart 1*B*) is one such complex which, in phase I clinical studies, was found to produce no significant renal damage, less vomiting than does cisplatin, and little or no high-frequency hearing loss (2). Hematological toxicity is dose limiting with CBDCA. Early results suggest that the efficacy and spectrum of activity of CBDCA are similar to those of cisplatin (2, 28).

During the Phase I study of CBDCA, it was noticed that hematological toxicity was exaggerated in patients with poor renal function (2). This suggested that a knowledge of the pharmacokinetic properties of this drug might be important for its safe usage. We have therefore carried out pharmacokinetic studies on patients with both normal and abnormal renal function.

MATERIALS AND METHODS

Patients and Sample Collection. Patients studied were receiving CBDCA as part of a Phase I or Phase II study (2). Informed consent was obtained from all patients. CBDCA was obtained free of charge from Bristol-Myers International Corp. (Brussels, Belgium) or from the National Cancer Institute (Bethesda, MD). CBDCA was given in doses ranging from 20 to 520 mg/sq m as a 1-hr i.v. infusion dissolved in 300 to 500 ml of 5% (w/v) dextrose. Renal glomerular filtration rates were determined in all patients by the technique of ^{51}Cr-EDTA clearance (3). No diuresis was induced and, with the exception of antiemetics (lorazepam and metoclopramide), no other drugs were given.

Blood samples were taken midinfusion, at the end of the infusion, and at the following approximate time points post-infusion: at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 12, 18, and 24 hr. The exact time of sampling was recorded in each case, and this value was used in all calculations. A single cumulative 0- to 24-hr urine sample was collected and stored at room temperature for up to 24 hr, after which an aliquot was removed and stored at −20°. Blood was collected into lithium heparin tubes (10 IU/ml) and centrifuged immediately (600 × g, room temperature, 10 min). The plasma was removed and cooled to 0°.

Total Platinum Analysis. Samples of plasma or urine were diluted in deionized water, and aliquots (10 to 100 μl) were analyzed for platinum using either a Perkin-Elmer Model 306 (Perkin-Elmer, Ltd., Beaconfield, Buckinghamshire, United Kingdom). or an Instrumentation Laboratories Model 357 (I. L. Ltd., Warrington, Cheshire, United Kingdom) atomic absorption spectrophotometer equipped with a heated graphite furnace. The conditions used were based on published methods (19) and optimized for each instrument. In all assays, 50 to 300 pmol of elemental platinum were analyzed, and quantification was achieved by comparison with platinum standards. Platinum analysis over this range was linear on both instruments (r > 0.999).

Free Platinum Analysis. Within 3 hr of collection, plasma samples were subjected to centrifugal ultrafiltration (1000 × g, 30 min, 4°) using Amicon CF50A ultrafiltration cones (Amicon, Ltd., High Wycombe, Buck-

[1] This work was supported by grants from the Medical Research Council and the Cancer Research Campaign, United Kingdom.

[2] To whom requests for reprints should be addressed.

Received July 11, 1983; accepted December 27, 1983.

[3] The abbreviations used are: CBDCA, *cis*-diammine-1,1-cyclobutane dicarboxylate platinum(II); GFR, glomerular filtration rate; HPLC, high-performance liquid chromatography; AUC, area under the plasma concentration *versus* time curve; DACCP, 4-carboxyphthalato(1,2-diammino-cyclohexane)platinum(II).

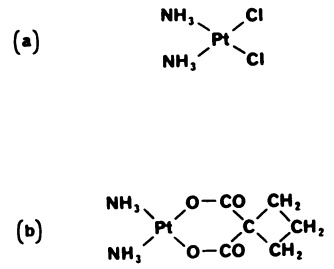

Chart 1. Structures of cisplatin (*a*) and CBDCA (*b*).

inghamshire, United Kingdom). The ultrafiltrate was analyzed for platinum by atomic absorption spectrophotometry and for CBDCA by HPLC.

Free CBDCA Analysis. Aliquots (10 μl) of plasma ultrafiltrates or urine were analyzed without pretreatment on a Waters Associates HPLC (Waters Associates, Milford, MA). All analyses were performed at room temperature, and plasma ultrafiltrates were analyzed within 6 hr of plasma collection. CBDCA was separated from endogenous components using a 25- x 0.46-cm column containing 5-μm Spherisorb silica (Phase Sep, Ltd., Queensferry, Clwyd, United Kingdom) and eluted isocratically with 90% acetonitrile/10% H_2O (v/v) at a flow rate of 2 ml/min. Acetonitrile was of low-UV grade and supplied by Rathburn Chemicals Ltd. (Walkerburn, Peebleshire, United Kingdom). CBDCA present in the eluate was detected by UV absorption at 225 nm, using either a Waters Associates M450 or M480 detector, and quantification was achieved by comparison of peak heights with standard curves prepared in control plasma and urine. The estimation of CBDCA by this method was linear over the range 10 to 100 μM for plasma and 10 to 1500 μM for urine ($r > 0.999$ in both cases). Representative chromatograms for the analysis of CBDCA in plasma ultrafiltrate and urine are given in Chart 2.

Pharmacokinetic Analysis. Following the end of the infusion, a 2-compartment open model was fitted to the plasma levels of total and free platinum using a computerized nonlinear least squares analysis with an error weighting of $1/(\hat{y} + y_i)^2$ (24). Due to the limit of sensitivity of the HPLC assay (10 μM), free CBDCA plasma levels could not be followed beyond 4 hr postinfusion; hence, a monoexponential equation was fitted to these data. AUCs were determined from the computer-generated fit and corrected for the period of the infusion (0 to 1 hr) by the trapezoidal rule. In patients in whom a 2-compartment model did not fit the data, because of insufficient data points, AUC values (0 to 24 hr) were determined by the trapezoidal rule.

Total and renal clearances of free platinum were calculated using the equations

$$\text{Total clearance} = \frac{\text{Dose}}{\text{Free platinum AUC } (0 - \infty)}$$

$$\text{Renal clearance} = \frac{\text{Platinum excreted in urine (0 to 24 hr)}}{\text{Free platinum AUC (0 to 24 hr)}}$$

Throughout the text, values are given as the mean, with the number of data points (*n*) given in brackets.

***In Vitro* Stability of CBDCA in Plasma and Urine.** CBDCA was added to plasma and urine samples collected from 6 normal subjects to give a final concentration of 100 μM in plasma and 1 mM in urine. These concentrations are representative of those seen in the plasma and urine of patients receiving therapeutic doses of CBDCA. Samples were incubated at 37° and, at various times (0 to 69 hr), aliquots were removed and analyzed for total platinum, free platinum, and free CBDCA.

RESULTS

***In Vitro* Stability of CBDCA in Plasma and Urine.** Incubation of CBDCA (100 μM, 37°) in plasma from normal subjects results in an exponential decline in both free platinum and CBDCA concentrations ($r > 0.95$; $p < 0.001$ for all analyses). Relatively little variation between individual samples was observed; mean free platinum $t_{1/2}$ was 30.3 ± 1.2 (S.E.) hr ($n = 6$), and mean CBDCA $t_{1/2}$ was 28.7 ± 1.0 hr ($n = 6$). In contrast, the rates of decomposition in urine showed considerable variation (range, 20 to ~460 hr). Individual data are given in Table 1. Samples of CBDCA (100 μM and 1 mM) incubated at 37° in deionized water for 69 hr showed no decomposition, as indicated by HPLC.

***In Vivo* Pharmacokinetics of CBDCA.** In the group of patients studied ($n = 19$) over the dose range 20 to 500 mg/sq m, peak plasma levels of total platinum and free platinum, achieved at the end of the infusion, correlated linearly with dose (total platinum, $r = 0.81$, $p < 0.001$; free platinum, $r = 0.939$, $p < 0.001$). Following the end of the infusion, plasma levels of total platinum and free platinum decayed biphasically with first-order kinetics. The half-lives determined for patients receiving 150 to 500 mg/sq m are given in Table 2, and an example of one patient is shown in Chart 3. In view of the prolonged nature of the total platinum β-phase, it was not possible, in most patients, to determine a half-life with any accuracy. The absolute range of values for total platinum $t_{1/2}^{\beta}$ was 399 to >1440 min.

As shown in Table 2, during the first 4 hr, the binding of

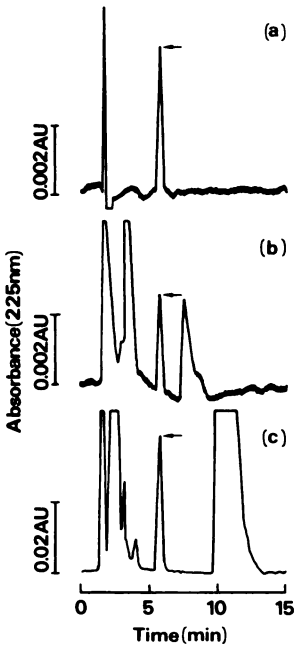

Chart 2. HPLC chromatograms illustrating the analysis of CBDCA. *a*, standard (100 μM); *b*, plasma ultrafiltrate (64 μM); *c*, urine (940 μM). ←, CBDCA. *AU*, absorbance units.

Table 1

In vitro decomposition of CBDCA in normal plasma and urine at 37°

Sample	Plasma: Free platinum $t_{1/2}$ (hr)	Plasma: CBDCA $t_{1/2}$ (hr)	Urine CBDCA $t_{1/2}$ (hr)
1	27	29	63
2	30	26	460
3	32	33	69
4	28	28	60
5	30	28	20
6	35	28	32
	30.3 ± 1.2[a]	28.7 ± 1.0	

[a] Mean ± S.E. of 6 experiments.

platinum to plasma proteins was minimal. In a study on 4 patients, most, if not all, of the free platinum during the initial phase was found to be in the form of unchanged CBDCA (Table 3). In these patients, the half-lives of free platinum and CBDCA were essentially identical, as shown in Table 3. An example of the total platinum, free platinum, and CBDCA levels in one patient during the initial phase is given in Chart 4. In contrast to the initial phase, by 24 hr postadministration, the majority of the plasma platinum was protein bound, 87 ± 4% (n = 11) (Table 2). During the 24-hr period following CBDCA administration, the free platinum AUC represented 68 ± 3% (n = 13) of the total platinum AUC.

In agreement with preliminary studies (2), the total platinum AUC was found to correlate linearly with dose (Chart 5). In those patients in whom particularly high AUC values were observed, this was usually attributable to impaired renal function, as indicated by reduced GFR (<60 ml/min). Thus, as shown in Charts 6 and 7, the total and renal clearances of free platinum correlated strongly with GFR. The slope of the regression line correlating the renal clearance of free platinum and GFR was less than unity, *i.e.*, 0.71 (95% confidence limits 0.26 to 1.16).

The proportion of the platinum administered appearing in the urine in the first 24 hr is shown for different dose levels in Table 4. The percentage of the dose excreted in the form of unchanged CBDCA is also given. This last value may have been an underestimate in some patients, since the chemical half-life of the compound in urine can be short (Table 1).

Table 2

Plasma half-lives and protein binding of platinum following CBDCA treatment

Dose (mg/sq m)	No. of patients	Total platinum $t_{1/2}^{\alpha}$ (min)	Free platinum $t_{1/2}^{\alpha}$ (min)	Free platinum $t_{1/2}^{\beta}$ (min)	% of protein bound (t = ~240 min)	% of protein bound (t = ~24 hr)
150	1	77	94	436	0	58
300	3	113	88	341	31	86
400	6	103	88	355	25	92
500	1	47	72	306	20	85
		98 ± 9[a]	87 ± 5	354 ± 48	24 ± 4	87 ± 4

[a] Mean ± S.E. of 11 experiments.

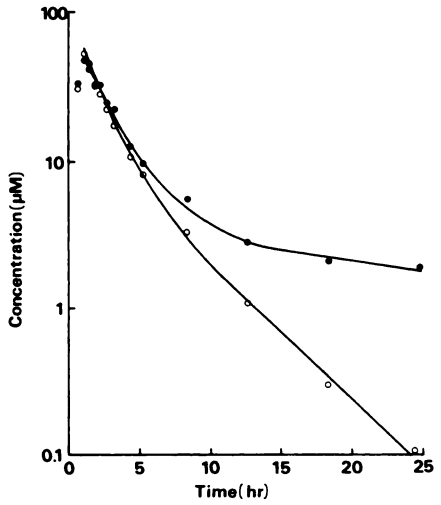

Chart 3. Plasma levels of total platinum (●) and free platinum (○) in a patient treated with CBDCA, 400 mg/sq m. *Lines* are the computer-generated fits.

DISCUSSION

CBDCA has been introduced into clinical use as a less toxic alternative to cisplatin. The pharmacokinetic properties of CBDCA are clearly very different from those of cisplatin and are summarized in Table 5. Many of these differences can be explained by a comparison of the chemical stability of the 2 compounds.

For both cisplatin and CBDCA, it is envisaged that, prior to exerting biological activity, the complexes must be converted to reactive platinum species by loss of one or both leaving groups, chloride and cyclobutane dicarboxylate, respectively. The aquo and hydroxy species thereby formed react avidly with nucleophilic sites in macromolecules. Cisplatin decomposes rapidly, half-lives of 1.5 to 3.6 hr being reported for its binding to plasma proteins *in vitro* at 37° (10, 23). CBDCA, on the other hand, is a stable complex which has an *in vitro* plasma half-life of 30 hr at 37°. The greater stability is probably due to the chelate effect arising from the bidentate cyclobutane dicarboxylate ligand (14). As a result of this stability, CBDCA remains intact for longer in body fluids, thereby allowing a greater proportion of the dose to be excreted in the urine. Therefore, relative to cisplatin, a large molar dose of CBDCA is required for the same biological activity (2, 28).

However, it is not immediately clear why CBDCA should be significantly less nephrotoxic than cisplatin. One hypothesis relates again to their relative stabilities. It is well known that the nephrotoxicity of cisplatin can be markedly reduced by the use of hydration and diuretics or by the prolonged infusion of the drug (22). More recently, it has been shown that, in experimental systems, chloruresis can also reduce the nephrotoxicity of cisplatin (8). Each of these maneuvers reduces the concentration of the reactive platinum species in the kidney tubule, the former by dilution, the latter by increasing the stability of cisplatin. The inherent stability of CBDCA would also serve to reduce the

Table 3

Postinfusion phase pharmacokinetics of total platinum, free platinum, and CBDCA

Patient	Dose (mg/sq m)	Period of observation (min)	Plasma half-life (min)			Free platinum (as % of total platinum)	CBDCA (as % of free platinum)
			Total platinum	Free platinum	CBDCA		
1	300	317	128	118	102	100	83
2	400	304	95	85	96	99	100
3	400	228	115	99	85	80	100
4	500	302	70	80	76	73	92
			102 ± 13[a]	96 ± 9	90 ± 6	88 ± 7	94 ± 4

[a] Mean ± S.E. of 4 experiments.

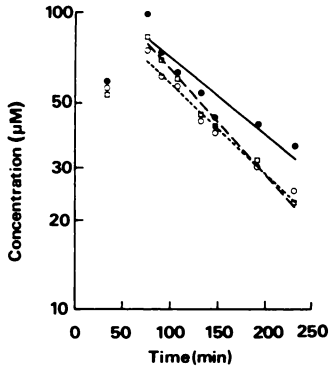

Chart 4. Plasma levels of total platinum (●——●), free platinum (○— —○), and CBDCA (□- - -□) in a patient receiving 400 mg/sq m CBDCA. *Lines* are the computer-generated fit.

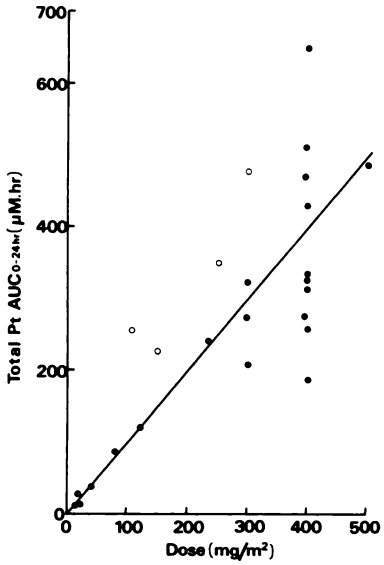

Chart 5. Correlation between dose of CBDCA and total platinum AUC (r = 0.759, $p < 0.0001$). ●, patients with normal renal function (GFR > 60 ml/min); ○, patients with impaired renal function (GFR < 60 ml/min).

relative concentration of reactive platinum species in the kidney tubule. Thus, despite the fact that higher total platinum levels will be present in the nephron following CBDCA, only a small fraction will be in the form of reactive platinum species.

Although, by the time of analysis, significant decomposition of CBDCA had occurred in the urine of most patients (Table 4), this may have been due to the delay which occurred during the collection period, *i.e.*, retention in the bladder and storage at room temperature for up to 24 hr. It should be noted that, when urine is collected from rodents receiving CBDCA by bladder cannulation, the majority of the platinum administered is excreted in the urine (85 to 90% of dose administered), mainly as the unchanged complex (70% of dose administered) (25). Thus, the nephrotoxicity of platinum complexes may relate primarily to the peak concentrations of reactive platinum species present in the kidney.

Data from preclinical and clinical studies with other platinum drugs apparently support this hypothesis. Pharmacokinetic studies with DACCP indicate that it binds rapidly to plasma proteins *in vivo* and is subject to only limited urinary excretion (17). DACCP is nephrotoxic in rats, dogs, and humans although, clinically, this is not the dose-limiting toxicity (17). In contrast, studies in dogs with the nonnephrotoxic complex *cis*-dichloro-*trans*-dihydroxybis(isopropylamine)platinum(IV) have shown that it binds slowly to plasma protein *in vitro* and *in vivo* and is excreted extensively in the urine, mainly as the unchanged complex at early time points (21). Thus, 2 nephrotoxic complexes, cisplatin and DACCP, are unstable *in vivo*, while 2 nonnephrotoxic complexes, CBDCA and *cis*-dichloro-*trans*-dihydroxy-bis(isopropylamine)platinum(IV), are not. Studies on a wider range of platinum drugs are obviously required to confirm this apparent correlation between chemical stability and nephrotoxicity.

A second possible explanation for the lack of nephrotoxicity displayed by CBDCA relates to its mechanism of renal clearance. Although cisplatin is probably subject to some degree of tubular secretion (6, 15, 16), it is unlikely that this is so with CBDCA, since the 95% confidence limits for the slope of the line correlating free platinum clearance and GFR only just exceeds unity

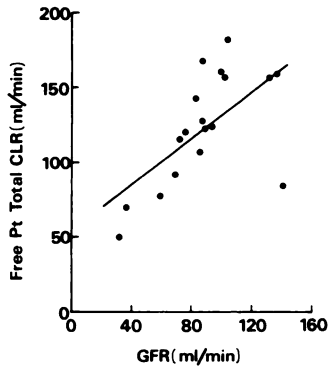

Chart 6. Correlation between GFR and free platinum plasma clearance (r = 0.611, p = 0.007).

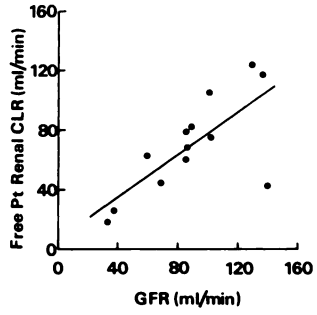

Chart 7. Correlation between GFR and free platinum renal clearance (r = 0.725, p = 0.005).

Table 4
Urinary excretion of CBDCA

Dose (mg/sq m)	No. of patients	Platinum excreted in 0–24 hr (% of dose)	CBDCA excreted in 0–24 hr (% of dose)
20	3	67	33
40	1	64	27
80	2	70	29
120	2	65	27
200	2	61	22
320	2	61	27
520	2	68	54
		65 ± 1[a]	32 ± 3

[a] Mean ± S.E. of 14 experiments.

Table 5
Comparative pharmacokinetics of cisplatin and CBDCA

	Total platinum $t_{1/2}^{\alpha}$ (min)	Total platinum $t_{1/2}^{\beta}$ (hr)	Free platinum $t_{1/2}^{\alpha}$ (min)	Free platinum $t_{1/2}^{\beta}$ (min)	% of protein bound (~4 hr postinfusion)	24-hr urinary platinum excretion (% of dose)	Free platinum renal CLR/GFR	Free platinum plasma CLR (ml/min)	*In vitro* free platinum $t_{1/2}$ (hr) (plasma, 37°)
Cisplatin[a]	18–37 (7, 10, 11, 13)	44–190 (7, 10, 11, 13, 20, 26)	22–78 (1, 5, 10, 11, 13, 20, 26)	Not seen	>90 (7, 10, 11, 13, 26)	16–35 (1, 7, 9–11, 20, 26)	0.9–1.9 (15, 16, 26)	400–600 (15, 26)	1.5–3.7 (10, 23)
CBDCA	98	6.7–>24	87	354	24	65	0.7	123	30

[a] Data for cisplatin are the ranges of mean values reported in the references.

(Chart 6). This is in agreement with studies in rats in which free platinum clearance following CBDCA and GFR were found to be equivalent (25). Thus, the renal clearance of CBDCA does not, apparently, involve a concentrative mechanism, whereas that for cisplatin probably does. The absence of such a mechanism for CBDCA may be related to its lack of nephrotoxicity.

In agreement with earlier work (2), this study has shown that patients with impaired renal function have greater than expected AUC for total platinum. Furthermore, it has been demonstrated that this is due to the reduced renal clearance of free platinum in these patients. In view of this, we feel that, to avoid untoward toxicity, it is necessary to reduce the dose of CBDCA when treating patients with poor renal function.

ACKNOWLEDGMENTS

The authors are greatly indebted to Dr. C. Barnard and P. Hydes (Johnson Matthey Research Centre, Sonning, Berkshire, United Kingdom) for advice and discussion and for assistance in developing the HPLC assay. They thank A. Robinson for typing this manuscript and also gratefully acknowledge the help of the medical and nursing staff of the Royal Marsden Hospital (Sutton, Surrey, United Kingdom) and the assistance of T. Root in formulating samples of CBDCA.

REFERENCES

1. Belt, R. J., Himmelstein, K. J., Patton, T. F., Bannister, S. J., Sternson, L. A., and Repta, A. J. Pharmacokinetics of non-protein-bound platinum species following administration of *cis*-dichlorodiammine platinum(II). Cancer Treat. Rep., *63:* 1515–1521, 1979.
2. Calvert, A. H., Harland, S. J., Newell, D. R., Siddik, Z. H., Jones, A. C., McElwain, T. J., Raju, S., Wiltshaw, E., Smith, I. E., Baker, J. M., Peckham, M. J., and Harrap, K. R. Early clinical studies with *cis*-diammine-1,1-cyclobutane dicarboxylate platinum(II). Cancer Chemother. Pharmacol., *9:* 140–147, 1982.
3. Chantler, C., Garnett, E. S., Parsons, V., and Veall, N. Glomerular filtration rate measurement in man by the single injection method using ^{51}Cr-EDTA. Clin. Sci. (Oxf.), *37:* 169–180, 1969.
4. Creaven, P. J., Mittelman, A., Pendyala, L., Tseng, M., Pontes, E., Spaulding, M., Moayeri, H., Madajewicz, S., Cowens, J. W., and Solomon, J. Phase I study of a new antineoplastic platinum analogue *cis*-dichloro-*trans*-dihydroxy-bis-isopropylamine platinum(IV) (CHIP). Proc. Am. Soc. Clin. Oncol., *1:* 22, 1982.
5. Crom, W. R., Evans, W. E., Pratt, C. B., Senzer, N., Denison, M., Green, A. A., Hayes, F. A., and Yee, G. C. Cisplatin disposition in children and adolescents with cancer. Cancer Chemother. Pharmacol., *6:* 95–99, 1981.
6. Daley-Yates, P. T., and McBrien, D. C. H. The mechanism of renal clearance of cisplatin [*cis*-dichlorodiammine platinum(II)] and its modification by furosemide and probenecid. Biochem. Pharmacol., *31:* 2243–2246, 1982.
7. DeConti, R. C., Toftness, B. R., Lange, R. C., and Creasey, W. A. Clinical and pharmacological studies with *cis*-diamminedichloroplatinum(II). Cancer Res., *33:* 1310–1315, 1973.
8. Earhart, R.H., Martin, P. A., Tutsch, K. D., Ërturk, E., Wheeler, R. H., and Bull, F. E. Improvement in the therapeutic index of cisplatin (NSC 119875) by pharmacologically induced chloruresis in the rat. Cancer Res., *43:* 1187–1194, 1983.
9. Frick, G. A., Ballentine, R., Driever, C. W., and Kramer, W. G. Renal excretion kinetics of high-dose *cis*-dichlorodiammine platinum(II) administered with hydration and mannitol diuresis. Cancer Treat. Rep., *63:* 13–16, 1979.
10. Gormley, P. E., Bull, J. M., LeRoy, A. F., and Cysyk, R. Kinetics of *cis*-dichlorodiammine platinum. Clin. Pharmacol. Ther., *25:* 351–357, 1979.
11. Gullo, J. J., Litterst, C. L., Maguire, P. J., Sikic, B. I., Hoth, D. F., and Woolley, P. V. Pharmacokinetics and protein binding of *cis*-dichlorodiammine platinum(II) administered as a one- or as a twenty-hour infusion. Cancer Chemother. Pharmacol., *5:* 21–26, 1980.
12. Harrap, K. R. Platinum analogues: criteria for selection. *In:* F. M. Muggia (ed.), Cancer chemotherapy, vol. 1, pp. 171–217. The Hague: Martinus Nijhoff Publishers, 1983.
13. Himmelstein, K. J., Patton, T. F., Belt, R. J., Taylor, S., Repta, A. J., and Sternson, L. A. Clinical kinetics of intact cisplatin and some related species. Clin. Pharmacol. Ther., *29:* 658–664, 1981.
14. Howe-Grant, M. E., and Lippard, S. J. Aqueous platinum(II) chemistry; binding to biological molecules. *In:* H. Sigel (ed.), Metal Ions in Biological Systems, vol. 11: Metal Complexes as Anticancer Agents, pp. 63–125. New York: Marcel Dekker, Inc., 1980.
15. Jacobs, C., Kalman, S. M., Tretton, M., and Weiner, M. W. Renal handling of *cis*-diamminedichloroplatinum(II). Cancer Treat. Rep., *64:* 1223–1226, 1980.
16. Jacobs, C., McGarry, K., Rich, L., and Weiner, M. W. Secretion of cisplatin and effects of probenecid: human and rat kidney slice studies. Proc. Am. Assoc. Cancer Res., *23:* 126, 1982.
17. Kelsen, D. P., Scher, H., Alcock, N., Leyland-Jones, B., Donner, A., Williams, L., Greene, G., Burchenal, J. H., Tan, C., Philips, F. S., and Young, C. W. Phase I clinical trial and pharmacokinetics of 4-carboxyphthalato-(1,2-diaminocyclohexane)platinum(II). Cancer Res., *42:* 4831–4835, 1982.
18. Krakoff, I. H. Nephrotoxicity of *cis*-dichlorodiammine platinum(II). Cancer Treat. Rep., *63:* 1523–1525, 1979.
19. Leroy, A. F., Wehling, M. L., Sponseller, H. L., Friauf, W. S., Solomon, R. E., Dedrick, R. L., Litterst, C. L., Gram, T. E., Guarino, A. M., and Becker, D. A. Analysis of platinum in biological materials by flameless atomic absorption spectrophotometry. Biochem. Med., *18:* 184–191, 1977.
20. Ostrow, S., Egorin, M. J., Hahn, D., Markus, S., Aisner, J., Chang, P., Leroy, A., Bachur, N. R., and Wiernik, P. H. High-dose cisplatin therapy using mannitol *versus* furosemide diuresis: comparative pharmacokinetics and toxicity. Cancer Treat. Rep., *65:* 73–78, 1981.
21. Pendyala, L., Cowens, J. W., and Creaven, P. J. Studies on the pharmacokinetics and metabolism of *cis*-dichloro-*trans*-dihydroxy-bis-isopropylamine platinum(IV) in the dog. Cancer Treat. Rep., *66:* 509–516, 1982.
22. Penta, J. S., Muggia, F. M., and Salem, P. A. Cisplatin in cancer therapy: optimisation of treatment regimens and toxicity protection. *In:* F. M. Muggia (ed.), Cancer Chemotherapy, vol. 1, pp. 149–169. The Hague: Martinus Nijhoff Publishers, 1983.
23. Repta, A. J., and Long, D. F. Reactions of cisplatin with human plasma and plasma fractions. *In:* A. W. Prestayko, S. T. Crooke, and S. K. Carter (eds.), Cisplatin. Current Status and New Developments, pp. 285–304,. New York: Academic Press, Inc., 1980.
24. Sampson, J. Nonlinear least squares, Program BMD X85. *In:* W. J. Dixon (ed.), University of California Publications in Automatic Computations, No. 3, BMD Biomedical Computer Programs X-Series Supplement, pp. 177–184. Berkeley, CA: University of California Press, 1970.
25. Siddik, Z. H., Newell, D. R., Jones, M., and Boxall, F. E. Pharmacokinetics of *cis*-diammine-1,1-cyclobutane dicarboxylate platinum(II) (CBDCA, JM8) in mice and rats. Proc. Am. Assoc. Cancer Res., *23:* 168, 1982.
26. Vermorken, J. B., Van Der Vijgh, W. J. F., Klein, I., Gall, H. E., and Pinedo, H. M. Pharmacokinetics of free platinum species following rapid, 3-hr and 24-hr infusions of *cis*-diamminedichloroplatinum(II) and its therapeutic implications. Eur. J. Cancer Clin. Oncol., *18:* 1069–1074, 1982.
27. von Hoff, D. D., Schilsky, R., Reichert, C. M., Reddick, R. L., Rozencweig, M., Young, R. C., and Muggia, F. M. Toxic effects of *cis*-dichlorodiammine platinum(II) in man. Cancer Treat. Rep., *63:* 1527–1531, 1979.
28. Wiltshaw, E., Evans, B. D, Jones, A. C., Baker, J. W., and Calvert, A. H. JM8: successor to cisplatin in advanced ovarian carcinoma? Lancet, *1:* 587, 1983.