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A model for ultrafilterable plasma platinum disposition in patients treated with cisplatin*

Phillip A. Reece[1], Irene Stafford[1], Jack Russell[2], Miriam Khan[1] andP. Grantley Gill[3]

[1] Department of Clinical Pharmacology, The Queen Elizabeth Hospital, Woodville Road, Woodville, SA, 5011, Australia
[2] Oncology Unit, Royal Adelaide Hospital, Adelaide SA, 5001 Australia
[3] University of Adelaide, Royal Adelaide Hospital, Adelaide SA, 5001 Australia

Summary. A model incorporating recent information regarding the specificity of a high-performance liquid chromatographic assay for "active" platinum in plasma ultrafiltrate, and the concept of mobile and fixed metabolites, was developed for cancer patients treated with cisplatin. Model parameters were determined using plasma and urinary platinum data obtained in 20 patients. It was assumed in the model that parent drug accounted for essentially all the platinum measured in plasma ultrafiltrate in the 2 h period immediately post infusion. At times greater than 4 h post infusion, platinum concentrations in plasma ultrafiltrate were assumed to be due entirely to reactive, mobile metabolites with possible cytotoxicity. The model accurately simulated platinum concentrations in plasma ultrafiltrate over a 24-h period following a 2-h infusion of 80 mg/m^2 of cisplatin to seven patients, 100 mg/m^2 to ten patients and 120 mg/m^2 to three patients.

Introduction

The introduction of cisplatin in the mid-1970s resulted in a significant decline in age-adjusted mortality statistics for testicular cancer, principally due to improved survival of patients with nonseminomatous cancer [9]. The drug is now used in the therapy of a number of tumors. Pharmacological studies of cisplatin have been extensive but complicated by the fact that the drug is highly chemically reactive and binds avidly to plasma and tissue proteins [6, 17]. The parent, *cis*-diamminedichloroplatinum(II), disappears rapidly from patient plasma; the t½ is approximately 30 min [9], and up to 40% of the dose may be recovered in urine in the first 2 h post infusion [13]. Due to difficulties in analytical methodology, the most commonly used measure of cytotoxic platinum-related material in plasma has been ultrafilterable plasma platinum (non-protein-bound platinum, UP). UP appears to have a t½ similar to that of the parent, at least for the first 2 h post infusion, but at later times probably consists primarily of low-molecular-weight metabolites [1, 3, 5, 7, 12]. At least some of these metabolites are likely to be cytotoxic, since the majority are readily converted to diethyldithiocarbamate (DDC) derivatives under the condition of the assay methods used [1, 2, 11].

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Offprint requests to: P. A. Reece

Both physiologically and nonphysiologically based pharmacokinetic models have been used to describe the disposition of cisplatin and its metabolites in man and animals [4, 6, 12, 17]. However, only recently has a physiological model been described which has incorporated information regarding the concept of separate fixed (protein-bound), and mobile (low-molecular-weight) metabolites [5]. It was the intention of the present studies to incorporate, wherever possible, the basic concepts of this model into a simple descriptive model of ultrafilterable platinum disposition in patients with cancer. A sensitive high-performance liquid chromatographic (HPLC) assay [11] was employed which allowed detection of UP for 24 h post infusion.

Materials and methods

Patients. Only patients receiving their first course of cisplatin who were expected to survive for at least 2 months and were able to give informed consent were eligible for the study. Twenty patients were studied (Table 1). All patients received uniform hydration, mannitol and antiemetic therapy, the details of which have been described previously [12]. Cisplatin was given in 1 l normal saline which was protected from light and infused over 2 h. All patients received the infusion at approximately the same time each day. A blood sample was collected prior to commencing the infusion and then serial samples were taken 10, 20 and 40 min and 1, 1.5, 2, 3, 4, 6, 12 and 24 h post infusion. Samples were collected into ethylene diamminetetraacetic acid (EDTA) and plasma immediately frozen until all collections were complete. The samples were then thawed and immediately centrifugally ultrafiltered using Amicon cones (type C25). Loss of cisplatin from plasma at −20° C under these conditions was less than 10% over 24 h. The presence of plasma proteins has been shown to reduce cisplatin stability by only approximately 30% [8]. Ultrafiltrate was stored frozen (−20° C) until analysis within 2 days. Urine specimens were collected each time the patient voided, the volume noted and a 10-ml aliquot stored frozen (−20° C) until analysis within 4 days.

Assay methods. Plasma ultrafiltrate and urinary platinum levels were quantitated by published HPLC methods [2, 11]. The limit of detection of the assay for platinum in ultrafiltrate was 2.5 ng/ml. The method involved precolumn derivatization with DDC, which converted only "active

Table 1. Patient characteristics

Patient no.	Sex	Age (years)	Surface area (m^2)	Dose (mg/m^2)	Other medication	Creatinine clearance (ml/min)
1	M	48	1.9	80	VINB	126
2	M	58	1.9	80	VINB	139
3	F	59	1.4	80	VINB	63
4	M	59	1.8	80	VINB	134
5	M	72	1.4	80	VINB	68
6	F	47	1.7	80	VINB	89
7	M	52	1.9	80	VINB	95
8	M	27	1.6	100	VINB, BLEO	75
9	M	50	2.1	100	VINB, BLEO	109
10	M	21	1.7	100	VINB, BLEO	110
11	M	36	1.8	100	VINB, BLEO	74
12	M	40	1.8	100	VINB, BLEO	80
13	M	37	1.8	100	VINB, BLEO	114
14	M	29	2.0	100	VINB	214
15	M	29	1.9	100	VINB, BLEO	146
16	M	34	1.9	100	VINB	78
17	M	32	1.7	100	VINB, BLEO	104
18	F	37	1.3	120	VINB	58
19	M	23	1.8	120	VINB, BLEO	84
20	M	48	1.8	120	–	103

VINB, vinblastine; BLEO, bleomycin

platinum" or labile platinum metabolites to the derivative [1]. Glutathione, cysteine and thiosulfate adducts of cisplatin were relatively unreactive towards DDC, and were therefore unlikely to interfere significantly in the assay. Methionine adducts do react and would be expected to be included in plasma ultrafiltrate and urinary levels of platinum if present in appreciable amounts [1]. Serum and urinary creatinine determinations were performed using a Boehringer-Mannheim colorimetric test kit.

Model development. LeRoy et al. described a flow-limited pharmacokinetic model for cisplatin in the beagle dog [6]. Evans used this model as the basis for the development of a physiological pharmacokinetic model for cisplatin disposition in children and adolescents with cancer [4]. The essential features of the model were that the parent drug was assumed to be rapidly distributed into an apparent volume which was estimated from the initial plasma concentration. Since the drug was given by 6-h infusion, the initial plasma concentration was estimated by correcting the concentration observed at the end of the infusion for the loss occurring during infusion. The parent was assumed to undergo two pathways of elimination, metabolism and renal excretion. The metabolites were distributed to plasma, skin, muscle, gut, liver and kidney and were finally eliminated via the kidney. More recently, King et al. described a sophisticated physiological model for cisplatin in several species [5] which incorporated observations regarding the concept of fixed or irreversibly protein-bound metabolites, and mobile or low-molecular-weight metabolites capable of crossing membranes and being eliminated in the kidney. Both parent drug and mobile metabolite were assumed to undergo flow-limited transport.

Information regarding tissue concentrations, individual tissue metabolic rate constants, tumor blood flow and volume were not available in the patients studied to allow ready application of the more complete model of King et al. [5]. The simple model shown in Fig. 1 was used in the present studies. It consisted of two compartments, a parent drug compartment (P) with volume (V_p) and concentration (C_p), and a mobile metabolite compartment (MM) with volume (V_{mm}) and concentration (C_{mm}). Parent drug was assumed to be eliminated by three pathways, namely renal clearance ($Cl_{r,p}$), metabolism to fixed metabolites or irreversibly protein-bound metabolites with rate constant K_{fm} and metabolism to mobile or low-molecular-weight metabolites with rate constant K_{mm}. Mobile metabolites were assumed to be eliminated only by renal clearance ($Cl_{r,mm}$), since they are likely to be less chemically reactive than the parent and therefore less able to bind to tissues. Both parent and mobile metabolites were assumed to be rapidly distributed into the apparent volumes V_p and V_{mm}. The drug was infused with a zero-order rate constant K_0 into the parent compartment P.

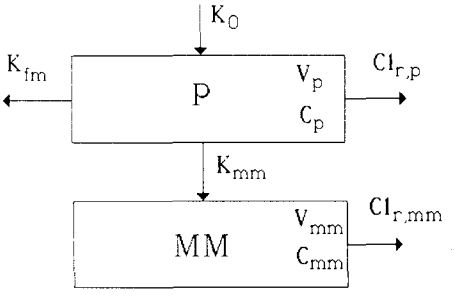

Fig. 1. Model for cisplatin disposition in patients with cancer. For explanation of symbols see text

Determination of model parameters

Renal clearance terms. Plasma ultrafiltrate concentrations of platinum obtained up to 2 h post infusion were assumed to represent essentially unchanged drug [10, 12, 15, 16].

This data was therefore used to estimate the renal clearance of unchanged drug ($Cl_{r,p}$) using Eq. 1:

$$Cl_{r,p} = \frac{E(-2 \text{ to } +2)}{AUC(-2 \text{ to } +2)} \quad (1)$$

where E(−2 to +2) was the amount of platinum excreted in urine during infusion and for the period corresponding most closely to 2 h postinfusion. AUC(−2 to +2) was the plasma AUC (area under the curve) of UP corresponding to the above urine collection interval. This was determined by fitting the postinfusion data to a conventional one-compartment model, correcting the resultant coefficient of the equation for the loss of drug occurring during infusion and then calculating the total AUC and the AUC from 2 h post infusion to infinity, using the equation coefficients. AUC(−2 to +2) was the difference between these two values.

At times greater than 4 h post infusion it could be assumed on the basis of the reported t½ for cisplatin [3, 10] that there was essentially no unchanged drug remaining in plasma ultrafiltrate. The renal clearance of mobile metabolites ($Cl_{r,mm}$) could therefore be estimated using data obtained from 4 to 24 h post infusion and Eq. 2:

$$Cl_{r,mm} = \frac{E(4 \text{ to } 24)}{AUC(4 \text{ to } 24)} \quad (2)$$

where E(4 to 24) was the amount of platinum excreted in urine in the collection period corresponding most closely to 4 to 24 h post infusion and AUC(4 to 24) was the corresponding AUC of UP for this period.

Volume terms. The volume of the parent compartment (V_p) was determined from Eq. 3:

$$V_p = \frac{Cl_t}{K_{e,p}} \quad (3)$$

Total clearance ($Cl_{t,p}$) in this relationship was determined using Eq. 4:

$$Cl_{t,p} = \frac{D_{iv}}{AUC}, \quad (4)$$

where D_{iv} was the administered dose of cisplatin and AUC the total AUC of UP determined from Eq. 5:

$$AUC = AUC(-2 \text{ to } +2) + \frac{C_{2.0}}{K_{e,p}}, \quad (5)$$

where $C_{2.0}$ was the concentration of UP 2 h post infusion. $K_{e,p}$, the first-order rate constant for elimination of the parent drug, was determined by nonlinear regression analysis using UP data obtained to 2 h post infusion. The volume of the mobile metabolite compartment (V_{mm}) was determined from Eq 6:

$$V_{mm} = \frac{Cl_{r,mm}}{K_{e,mm}}, \quad (6)$$

where $K_{e,mm}$, the first-order rate constant for elimination of mobile metabolite, was determined by nonlinear regression analysis of UP data from 4 to 24 h post infusion.

Metabolic rate constants. The combined metabolic rate constant K, comprising that due to metabolism to fixed metabolites (K_{fm}) and that due to mobile metabolites (K_{mm}) was determined from Eq. 7:

$$K = K_{fm} + K_{mm} = \frac{Cl_t - Cl_{r,p}}{V_p} = \frac{Cl_{m,p}}{V_p}, \quad (7)$$

where $Cl_{m,p}$ was the total metabolic clearance of the parent. Individual values of K_{fm} and K_{mm} could not be directly estimated. However, King et al. [5] have suggested that the ratio of nonprotein thiol groups to protein thiol groups in plasma may be a determinant of the relative contribution of metabolism to fixed and mobile metabolites. In plasma this ratio was 0.05 [5], suggesting that for a K value of 0.0146 (80 mg/m^2), individual values of K_{fm} and K_{mm} would be 0.0139 and 0.00073 respectively. However, in the present studies, a two-fold smaller value of 0.003 min^{-1} for the rate constant K_{mm} provided the best simulation of the observed data.

Model simulations. Estimates of the above parameters were obtained for each patient. Mean values were then obtained for each group of patients, receiving 80, 100 and 120 mg/m^2 doses. The mean values were used in model simulations at each dose level. The model was described by the following differential equations (Eqs. 8, 9), which were simultaneously solved using the program of Williams and Naringrekar [18] to simulate plasma ultrafiltrate concentrations of parent drug (C_p) and mobile metabolite (C_{mm}):

$$\frac{dC_p}{dt} = \frac{K_o - Cl_{r,p} * C_p - K * V_p * C_p}{V_p} \quad (8)$$

$$\frac{dC_{mm}}{dt} = \frac{K_{mm} * V_p * C_p - Cl_{r,mm} * C_{mm}}{V_{mm}} \quad (9)$$

Results

UP plasma levels were detectable in all patients for the entire 24-h duration of the study. Mean (SD) levels 24 h post infusion in patients receiving doses of 80, 100 and 120 mg/m^2 were 5.87 (2.60), 6.76 (3.53) and 9.31 (5.41) ng/ml respectively. Individual and mean model parameters for parent and mobile metabolites at each dose level are shown in Tables 2 and 3 respectively. The mean parameters at each dose level were used to simulate plasma concentrations of UP for the model described. Simulated and observed mean (±SE) UP plasma concentrations following infusion of 80 mg/m^2 of cisplatin to seven patients, 100 mg/m^2 to ten patients and 120 mg/m^2 to three patients are shown in Fig. 2. Simulated plasma concentrations of parent drug rose rapidly and then declined, with a t½ of 33.3, 27.4 and 28.2 min at the 80, 100 and 120 mg/m^2 dose levels respectively. This corresponded to an observed t½ (mean ±SD) of UP of 35.6±2.9 min, 27.4±4.7 min and 29.0±4.4 min for the first 2 h post infusion at the same dose levels. The model predicted that plasma levels of the parent drug would be negligible at times greater than 3 h post infusion. At these times mobile metabolites were the sole contributor to UP levels. Simulated plasma concentrations of this latter phase gave a t½ of 22.8, 19.1 and 14.8 h for mobile metabolites at the 80, 100 and 120 mg/m^2 dose levels. This corresponded to an observed t½ of 20.7±8.7 h, 13.1±8.3 h and 25.9±11.3 h for UP in the period 4 to 24 h post infusion at each dose level. Only three patients received the

Table 2. Model parameters for parent[a]

Patient no.	$K_{e,p}$ (min^{-1})	K (min^{-1})	$Cl_{t,p}$ ($ml/min/m^2$)	$Cl_{r,p}$ ($ml/min/m^2$)	$Cl_{m,p}$ ($ml/min/m^2$)	V_p (ml/m^2)
			80 mg/m²			
1	0.0197	0.0142	1047	295	752	52632
2	0.0217	0.0166	910	215	695	42053
3	0.0206	0.0138	619	205	414	30000
4	0.0195	0.0132	1904	609	1295	97777
5	0.0199	0.0170	672	97.9	574	33857
6	0.0168	0.0136	1120	209	911	67059
7	0.0190	0.0136	1067	345	722	53158
Mean	0.0196	0.0146	1040	302	766	51900
SD	0.0015	0.0016	424	162	280	22400
			100 mg/m²			
8	0.0206	0.0156	2098	506	1592	101875
9	0.0265	0.0240	1153	108	1045	43619
10	0.0227	0.0156	1443	449	994	63529
11	0.0258	0.0200	1349	305	1044	52278
12	0.0228	0.0185	1084	205	879	47556
13	0.0383	–	–	427	–	–
14	0.0292	0.0220	841	205	637	28900
15	0.0215	0.0139	1940	693	1247	90000
16	0.0240	0.0181	589	144	445	24527
17	0.0295	0.0210	499	144	355	16882
Mean	0.0261	0.0247	1220	318	915	52100
SD	0.0053	0.0017	552	181	391	28900
			120 mg/m²			
18	0.0239	0.0214	741	78.5	664	31077
19	0.0267	0.0220	1275	221	1054	47833
20	0.0236	0.0179	1219	296	923	51667
Mean	0.0247	0.0204	1080	199	880	43500
SD	0.0017	0.0022	293	110	199	10900
			All			
Mean	0.0236	0.0175	1140	288	855	51400
SD	0.0040	0.0034	461	171	321	24000

Model parameters determined using UP plasma concentrations during and up to 2 h post infusion
$K_{e,p}$, elimination rate constant of parent; K, total metabolic rate constant = Kfm + Kmm; $Cl_{t,p}$, total clearance of parent; $Cl_{r,p}$, renal clearance of parent; $Cl_{m,p}$, metabolic clearance of parent; V_p, volume of parent compartment

120 mg/m² dose and the lack of agreement with the observed and predicted t½ of mobile metabolites may be due in part to the use of mean estimates of parameters for which there was large interpatient variability between the three patients at this dose level.

Comparison of model parameters between patients in each of the three dosage groups was undertaken using analysis of variance. The only parameters shown to differ significantly among the dose levels were the rate constant for elimination of parent drug ($K_{e,p}$) and the total metabolic rate constant of parent drug (K). These parameters were both significantly smaller at the 80 mg/m² dose level ($P<0.025$ and $P<0.01$ respectively). The difference between the 80 and 100 mg/m² doses was 33% for $K_{e,p}$ and 69% for K.

Mean values of the volume terms V_p (volume of parent compartment) and V_{mm} (volume of metabolite compartment) in all patients differed by only 6% ($P>0.05$) suggesting that although calculated independently, these two parameters could be considered equivalent. The magnitude of this volume term in each case was considerably greater than the sum of the individual physiological volumes for plasma, kidney, liver, gut, skin and muscle estimated on the basis of total body weight and surface area equations described by Evans et al. [4].

Discussion

A model for UP disposition in patients is described which incorporates recent information regarding platinum metabolism and the specificity of an HPLC method for "active" platinum in plasma ultrafiltrate. The model accurately simulated UP plasma levels in patients at dose levels of 80, 100 and 120 mg/m² over a 24 h period post infusion. The observed and predicted half-lives of parent drug and mobile metabolite were in close agreement. Using analyti-

Table 3. Model parameters for mobile metabolites

Patient no.	$K_{e,mm}$ (min^{-1})	$Cl_{r,mm}$ (ml/min/m^2)	V_{mm} (ml/m^2)
	80 mg/m^2		
1	0.000483	35.1	72523
2	0.000200	21.7	108684
3	0.000717	38.6	53821
4	0.000383	15.4	40145
5	0.000500	26.8	53571
6	0.000800	22.5	28088
7	0.000833	57.9	69474
Mean	0.000559	31.1	60900
SD	0.000234	14.2	26151
	100 mg/m^2		
8	0.000867	17.4	20120
9	0.000450	14.1	31429
10	0.00137	57.9	42353
11	0.00283	17.7	62549
12	0.00130	65.0	50000
13	0.00208	14.6	6987
14	0.00650	22.5	34615
15	0.000800	52.6	65789
16	0.000583	8.63	14797
17	0.000417	39.9	95718
Mean	0.000880	31.0	42436
SD	0.000554	20.9	26971
	120 mg/m^2		
18	0.000300	52.2	17410
19	0.000667	8.89	13333
20	0.000367	32.6	88939
Mean	0.000445	31.2	39894
SD	0.000195	21.7	42523
	All		
Mean	0.000703	31.1	48517
SD	0.000448	17.9	28958

Model parameters determined using UP plasma concentrations from 4 to 24 h post-infusion
$K_{e,mm}$, elimination rate-constant of mobile metabolites; $Cl_{r,mm}$, renal clearance of mobile metabolites; V_{mm}, volume of mobile metabolite compartment

cal methodology specific for unchanged cisplatin, Patton et al. [10] obtained a mean t½ for cisplatin of 27.9 min in six patients after a 100 mg/m^2 i. v. bolus and Reece et al. [13] obtained a mean t½ of 31.6 min in seven patients after 100 mg/m^2 i. v. infusion. This was in close agreement with the mean t½ of 29.4 min for parent drug estimated from UP plasma levels obtained up to 2 h post infusion in this study. These results suggest that UP plasma levels obtained up to 2 h after a 2 h infusion consist primarily of unchanged drug. Other studies support this possibility [15, 16]. However, at times greater than 4 h post infusion, parent drug levels were assumed to be negligible. At this time, "active" or mobile, low-molecular-weight metabolites capable of reacting with the assay derivatizing reagent, DDC, were assumed to account for the observed UP plasma level. This assumption was necessary since cisplatin incubat-

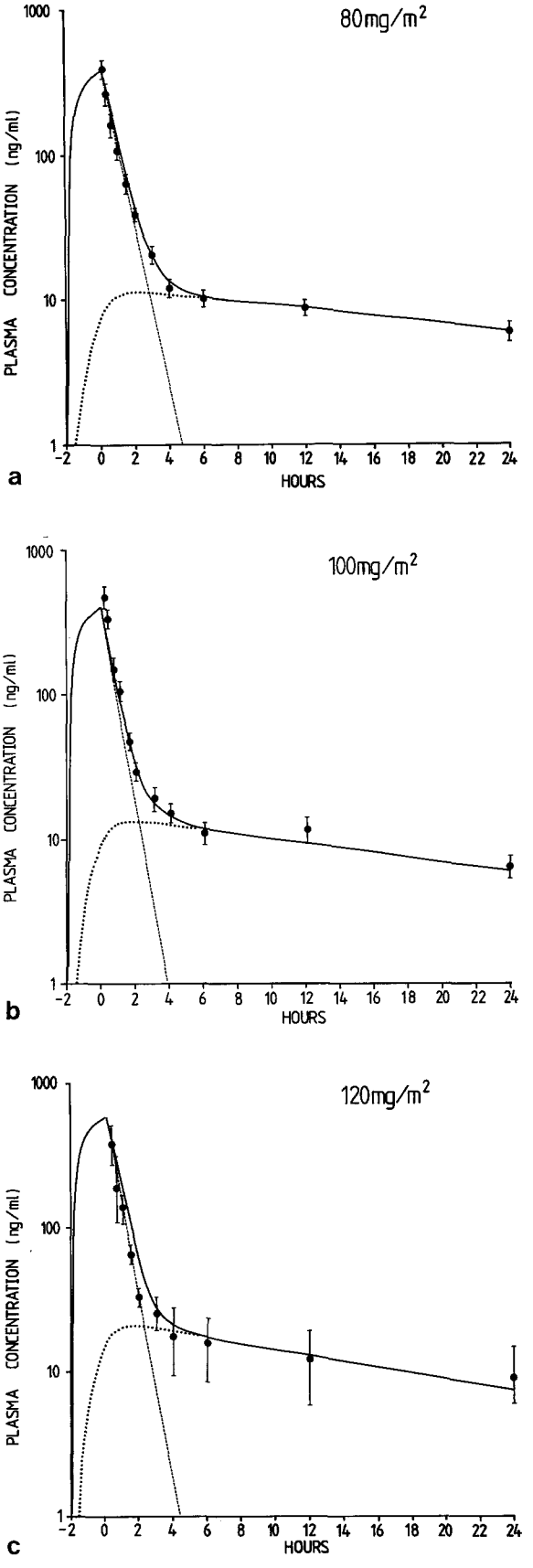

Fig. 2a–c. Observed mean (±SE) ultrafilterable platinum plasma concentrations and simulated concentrations of parent drug (-------), mobile metabolites (· · · · · · ·) and ultrafilterable platinum (———) in patients with cancer at dose levels of **a** 80 mg/m^2 (n=7), **b** 100 mg/m^2 (n=9) and **c** 120 mg/m^2 (n=3)

ed in plasma at 37° C in vitro had t½ of only 90 min [11] and would be expected to be essentially completely converted to metabolites in vivo at times greater than 4 h post infusion. LeRoy et al. [7] studied quantitative changes in cisplatin speciation in excreted urine with time after i. v. infusion to man and found that the ratio of the two predominant species changed markedly with time after completion of the infusion. Riley et al. obtained similar results [14]. Daley-Yates and McBrien [3] demonstrated the presence of a number of cisplatin metabolites in plasma ultrafiltrate and urine after administration of the drug to animals. However, Andrews et al. [1] have shown that only the most reactive and potentially cytotoxic of these are expected to contribute to the levels measured using the derivatization assay method employed in these studies [11]. The DDC derivatization assay method used here may therefore have an applied advantage over methods which measure only cisplatin or include inactive metabolites.

The model described in these studies assumed that both parent drug and mobile metabolites distributed rapidly and uniformly throughout parent and mobile metabolite "compartments" respectively. A similar assumption was made by Evans et al. [4] in pharmacokinetic modelling of parent cisplatin disposition in children and adolescents with cancer. Very frequent blood sampling would have been required in the present studies to define an early distribution phase, and hence provide the basis for a more complex model involving distribution to various organs and tissues. The magnitude of the volume terms estimated for parent and mobile metabolites suggested that both were widely distributed throughout the body and were not restricted to a relatively limited plasma compartment.

The estimated metabolic rate constant for parent drug in this study (K) was smaller in patients receiving the 80 mg/m^2 dose. The reason for this difference was not ascertained, but may have been related to the fact that patients at the higher dose levels received bleomycin in combination with cisplatin and vinblastine. A pharmacokinetic interaction between cisplatin and bleomycin could therefore be postulated, although the mechanism is unknown.

The present model differs from that of Evans et al. [4] in that separate physiological compartments were used in the latter to describe the disposition of cisplatin metabolites throughout the body. Cisplatin metabolites in this context referred to the difference between total platinum and cisplatin plasma levels. Parent cisplatin as referred to by Evans et al. [4] was total ultrafilterable plasma platinum, and was not quantitated with sufficient sensitivity to allow detection of the terminal phase seen in the present studies. Nevertheless, the time course of ultrafilterable platinum concentrations in the study of Evans et al [4] over the period up to 2 h post infusion was similar to that in the present study.

We recently reported the results of a pharmacokinetic study in patients with ovarian cancer where analytical methodology specific for unchanged cisplatin was employed [13]. Values of cisplatin total clearance (253 ± 48 ml/min/m^2), renal clearance (56.8 ± 17.3 ml/min/m^2), and volume of distribution (11.5 ± 2.7 ml/min/m^2) were considerably smaller than those obtained in the present study. The patients were a smaller (mean surface area: 1.58 ± 0.22 m^2) and older (mean age: 56 ± 12 years) group of females with relatively poor renal function (creatinine clearance: 38 ± 16 ml/min/m^2) who received no concurrent cytotoxic therapy. We have performed similar studies (unpublished) in younger male patients with germ cell cancer and higher values of cisplatin clearance and volume of distribution were obtained.

The development of a satisfactory model for ultrafilterable platinum disposition in patients is important, since this is the species usually quantitated in pharmacokinetic studies of cisplatin. It is also probably the most relevant quantitative measure if, as has been supposed, it comprises active cytotoxic metabolites as well as the parent drug. The observation in these studies of persistent low levels of such species up to 24 h post infusion may therefore be of clinical importance.

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