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Original Paper

Cisplatin Pharmacokinetics in Children with Cancer

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Cisplatin is an important drug in the treatment of a number of paediatric cancers yet, despite widespread use, there are only very limited data on the pharmacokinetics of the drug in children. Cisplatin pharmacokinetics were studied in 21 patients following a 24 h infusion of 50–120 mg/m^2 cisplatin. Total and free platinum (Pt) levels in plasma and Pt in urine, were measured by atomic absorption spectrophotometry. Pharmacokinetic parameters were determined by non-compartmental and compartmental analyses. There was 3-fold interpatient variability in free drug exposure (area under the plasma concentration versus time curve—AUC) for a given surface area-based dose of cisplatin. The mean (± SD) pharmacokinetic parameters for free Pt were: AUC 0.47 ± 0.13 mg/ml.min/100 mg/m^2, V_{dss} 12.5 ± 2.7 l/m^2, $t_{1/2}$ 39 ± 9 min, Ke 0.019 ± 0.006 min^{-1}, Cl_{renal} 62 ml/min/m^2, Cl_{total} 233 ± 455 ml/min/m^2, Cp_{ss} 0.31 ± 0.09 μg/ml. The total free Pt clearance was 1.5–5.8-fold higher (3.4 ± 1.0) than the glomerular filtration rate (GFR). The renal clearance of cisplatin was not related to GFR and cisplatin was subject to only limited urinary excretion (27% administered dose 0–48 h), indicating that there are other important pathways of clearance beside renal elimination. Patient and treatment heterogeneity precluded the investigation of pharmacokinetic–pharmacodynamic relationships; however, the degree of interpatient pharmacokinetic variability observed suggests that body surface area-based dosing of cisplatin in children is not satisfactory. © **1997 Elsevier Science Ltd.**

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INTRODUCTION

CISPLATIN IS still an important drug in the management of a number of malignancies in children, in particular neuroblastoma [1], germ cell tumours [2] and osteosarcomas [3]. Although highly active, cisplatin has a number of toxicities, most notably emesis, ototoxicity, nephrotoxicity and neurotoxicity [4]. As with any drug, the activity and toxicity of cisplatin depend upon both pharmacokinetic and pharmacodynamic factors [5], and in adults a number of pharmacokinetic–pharmacodynamic correlations have been found from studies of free and total platinum (Pt) species in blood plasma after various cisplatin treatment regimens. Thus, it has been suggested that free or total Pt plasma concentrations, either AUC or peak plasma level, are determinants of renal toxicity [6–10], myelosuppression [8, 11], emesis [12] and response [11]. In contrast to adults, the pharmacokinetics of cisplatin in children have been the subject of only a few studies [13–15]. Furthermore, the limited number of patients investigated severely restricts the confidence that can be placed in the generality of the results obtained. The objective of the current study was to describe cisplatin pharmacokinetics in children receiving the drug at doses ranging from 50 to 120 mg/m^2 given as a 24 h infusion in combination with other chemotherapeutic agents.

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PATIENTS AND METHODS

Patient selection and treatment

Twenty-one children and adolescents receiving cisplatin at the Children's Cancer Unit of the Royal Victoria Infirmary (Newcastle, U.K.) were entered into this study. The study protocol was approved by the Newcastle Health Authority and University of Newcastle upon Tyne Joint Ethics Committee. All patients and/or their parents gave informed consent prior to entering the study. The age, sex, body weight, surface area, diagnosis, glomerular filtration rate (GFR),

serum albumin, course studied, details of prior cisplatin treatment, concomitant chemotherapy and cisplatin dose for each patient are given in Table 1. Cisplatin was administered as a 24 h infusion through one lumen of a central venous catheter at doses of 50–120 mg/m^2 with hydration at 3000 ml/m^2/day for 2 days.

Blood samples (3 ml) were obtained from a central line immediately before the beginning and at 0.5, 1.0, 2.0, 4.0, 6.0, 18.0 h into the infusion, at the end of infusion and 0.5, 1.0, 1.5, 2.0, 24 and 48 h thereafter. Blood was collected into tubes pre-cooled on ice and centrifuged immediately at 1000*g* for 10 min at 4°C. Plasma was then removed and 1 ml placed in an Amicon Centrifree micropartition unit (MW 30 000 cut-off, Amicon Ltd, Stonehouse, U.K.) and centrifuged at 2000*g* for 10 min at 4°C. Plasma ultrafiltrate and plasma were stored at −20°C until analysed (< 1 month) for free and total platinum content.

In 12 children, urine was collected for 6-h periods during and for the 24 h following treatment and stored at −20°C until analysed for platinum content.

The GFR was estimated prior to the administration of cisplatin from the plasma clearance of ^{51}Cr-EDTA estimated from the one compartment analysis of plasma ^{51}Cr-EDTA concentration versus time data [16].

Platinum analyses

Plasma ultrafiltrate, whole plasma and urine were analysed for Pt by flameless atomic absorbtion spectroscopy by use of a graphite tube atomiser (PU9100, ATI Unicam, Cambridge, U.K.) according to a previously published procedure [17]. A standard curve covering the range of 0.05–0.2 μg/ml cisplatin was analysed with each assay. The accuracy of this curve was determined by use of an independent quality control sample at a cisplatin concentration of 0.1 μg/ml which was stored at −20°C and intra- and interassay coefficients of variation were < 10%. All concentrations are expressed as μg cisplatin equivalent/ml.

Pharmacokinetic analysis

Free Pt pharmacokinetic parameters: non-compartmental and compartmental pharmacokinetic analyses were performed, and the non-compartmental analysis, based on statistical moment theory [18], provided the following kinetic parameters:

The AUC by the trapezoidal rule, with extrapolation to infinity,

$$\mathrm{AUC} = \sum\left[\frac{(C_{n-1}+C_n)(t_n - t_{n-1})}{2}\right] + \frac{C_f}{K_e}$$

where C is the concentration at time t for plasma samples at n time points. C_f is the plasma concentration at the last time point at which Pt was determined and K_e is the terminal plasma rate constant determined by fitting a one-compartment model using ADAPT program as described below,

area under moment curve (AUMC),

$$\mathrm{AUMC} = \sum\left(\frac{[(C_{n-1}\times t_{n-1})+(C_n \times t_n)]\times(t_n - t_{n-1})}{2}\right) + \frac{C_f}{(K_e)^2}$$

total plasma clearance (CL),

$$\mathrm{CL_{total}} = \frac{\text{dose}}{\mathrm{AUC}}$$

and renal clearance of free platinum,

$$\mathrm{CL_{renal}} = \frac{\text{Urine Pt}_{(0-24\,h)}}{\text{Plasma-free PtAUC}_{(0-24\,h)}}$$

Table 1. Characteristics of children studied

Patient	Age (years)	Sex	BW (kg)	Surface area (m^2)	Diagnosis	GFR (ml/min/1.73 m^2)	Serum albumin (g/l)	Course studied/ prior cisplatin dose (mg/m^2)	Concurrent treatment	Dose (mg/m^2)
1	9.3	M	19.3	0.82	OS	152	39	2/100	CP/DOX	100
2	9.1	M	38.8	1.26	OS	83	43	1/0	CP/DOX	100
3	7.5	M	22.3	0.94	NB	175	33	2/0	CP/O	80
4	19.3	F	68.8	1.75	OS	99	35	2/100	CP/DOX	100
5	4.6	F	19.1	0.78	OS	165	39	3/200	CP/DOX	100
6	0.5	M	8.4	0.41	A	160	40	8/53	CP/O	50
7	17.5	M	75.5	1.92	MFH	81	38	4/300	CP/DOX	100
8	3.8	M	13.7	0.6	NB	138	34	2/0	CP/O	80
9	5.3	M	16.9	0.75	NB	145	37	2/0	CP/O	80
10	5.4	F	18	0.78	MOC	140	—	2/100	CP/DOX/CY	100
11	14.0	M	46.3	1.49	SCC	118	42	1/0	CP/5-FU	100
12	1.7	M	11.5	0.52	NB	139	45	1/0	CP/O	80
13	13.5	F	42.7	1.63	NE	101	43	2/120	CP/DOX	120
14	18.5	M	62.7	1.8	OS	120	48	1/0	CP/DOX	100
15	18.3	M	43.2	1.4	NB	127	34	2/0	CP/O	80
16	17.9	F	45.4	1.45	OS	92	36	1/0	CP/DOX	100
17	8.6	F	21.6	0.87	OS	141	46	1/0	CP/DOX	100
18	11.3	F	46.9	1.5	OS	124	42	1/0	CP/DOX	100
19	15.0	F	71.3	1.85	OS	94	44	1/0	CP/DOX	100
20	2.4	M	12.7	0.57	NB	97	31	3/80	CP/O	100
21	1.8	M	13.5	0.54	NB	112	—	3/80	CP/O	80

F, female; M, male; NB, neuroblastoma; OS, osteosarcoma; A, high-grade astrocytoma; MFH, malignant fibrous histiocytoma of bone; MOC, mucoepidermoid carcinoma of parotid gland; SCC, squamous cell carcinoma; NE, neuroendocrine tumour; CP, cisplatin; O, vincristine; CY, cyclophosphamide; 5-FU, 5-fluorouracil; DOX, doxorubicin; BW, body weight; GFR, glomerular filtration rate.

Pharmacokinetic parameters were also determined by fitting a one-compartment open model with exponential decay using the ADAPT programme (Release III) kindly supplied by Drs D'Argenio and Schumitzky (Biomedical Simulations Resource, University of Southern California, Los Angeles, California, U.S.A.). A one-compartment pharmacokinetic model with constant-rate intravenous infusion was fitted to each data set using the maximum likelihood (ML) estimator and data were weighted using the inverse variance of the output error. The following parameters were estimated: total plasma clearance (CL_{total}), volume of distribution (VD_{ss}) elimination rate constant (K_e), half-life ($t_{1/2}$) and Cp_{ss} ($Cp_{ss} = K_0/(VD_{ss} \times K_e)$, where K_0 is the drug infusion rate).

RESULTS

Free Pt and total Pt concentrations were measured in the plasma of 21 patients following the administration of cisplatin at doses of 50–120 mg/m^2 as a 24 h infusion. Figure 1 illustrates total and free Pt concentrations in the plasma of a child during and after a 24 h infusion of 100 mg/m^2 cisplatin. Plasma free Pt concentrations during the infusion reached a plateau with steady-state concentrations of 0.31 ± 0.09 (0.20–0.57) μg/ml (mean ± SD (range)), and declined mono-exponentially to below the limit of detection (0.05 μg/ml) within 2–3 h of completion of the infusion. The pharmacokinetic parameters of the 21 patients determined by non-compartmental and compartmental analyses are listed in Table 2, the two methods giving very similar results.

Peak plasma total Pt concentrations of 4–6 μg/ml were observed at the end of the infusion. The initial disappearance of total platinum was followed by a secondary peak 1–3 h after the infusion ended in 17/21 cases (Figure 1(b)). Overall, the time course of the total Pt concentrations was more complex than the free Pt levels and was not described by a simple exponential model.

The relationship between a given surface area-based dose of cisplatin and the free cisplatin AUC was investigated (Figure 2). The normalised clearance varied over a 2.7-fold (ml/min/m^2) or 3-fold (ml/min/kg) range (Table 2), implying that much of the variability in cisplatin clearance is the result of factors other than, or unrelated to, body size as measured either by surface area or body weight.

Satisfactory 0–48 h urine collections were possible in 12 children and the mean urinary Pt elimination during this period was 27 ± 7% of the total dose administered, indicating that cisplatin is subject to only limited direct urinary excretion and that there are other pathways of clearance besides renal elimination. The total free Pt plasma clearance (CL_{total}) was not related to GFR, and the free Pt total plasma clearance was 1.5–5.8 times greater than GFR (mean ratio ± SD; 3.4 ± 1.0, $n = 21$). Similarly, for the 12 children in whom urine collections were possible, there was no relationship between free Pt renal clearance and GFR, the ratio of cisplatin renal clearance to GFR being 0.91 ± 0.44. Finally, there was no dependency of free Pt plasma clearance on serum albumin levels, the course of therapy on which cisplatin pharmacokinetics were studied or the cumulative cisplatin dose previously given to the child.

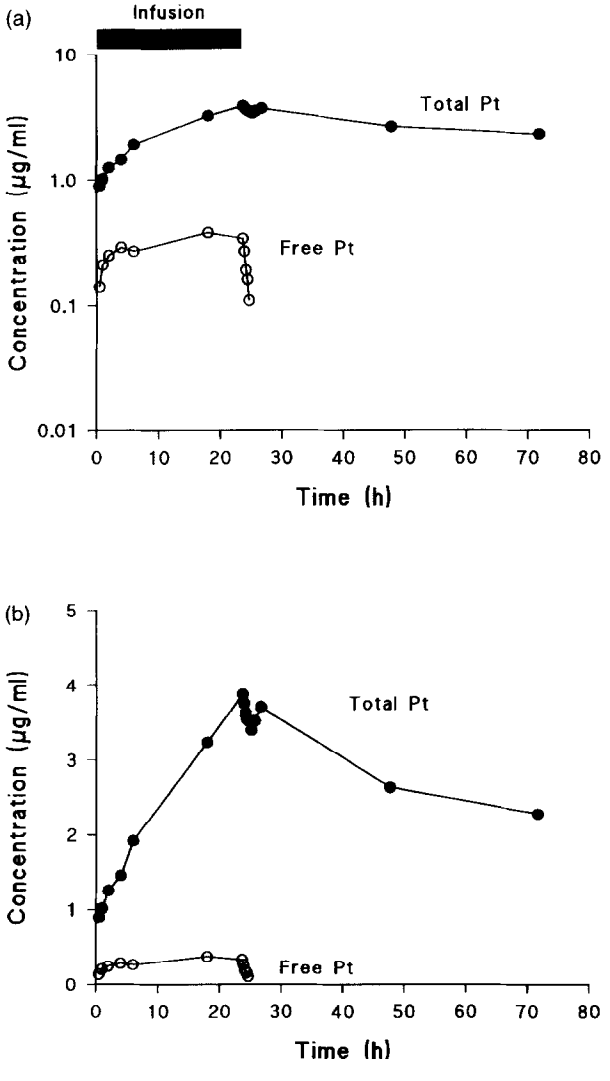

Figure 1. Plasma-free and total Pt concentrations (cisplatin equivalents) in a child treated with 100 mg/m^2 as a 24 h i.v. infusion. (a) Concentrations plotted on a logarithmic scale. (b) Concentrations plotted on a linear scale to illustrate the secondary rise in total Pt concentrations.

DISCUSSION

The aims of the present study were to define the pharmacokinetics of cisplatin in children and investigate the interpatient variability of cisplatin disposition following a 24 h

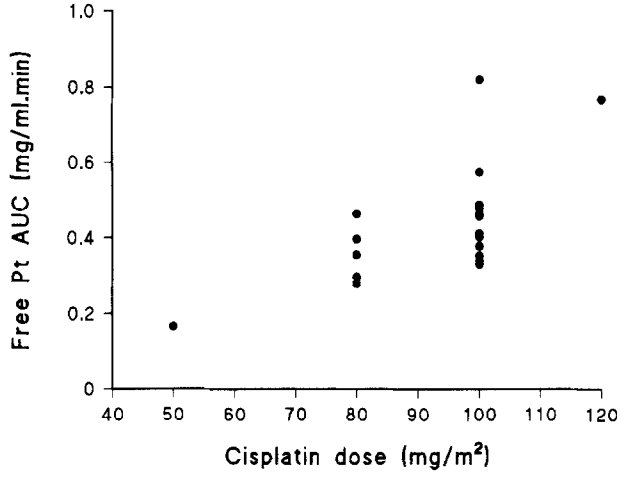

Figure 2. Relationship between administered cisplatin dose and plasma-free Pt AUC. AUC values were determined by a model independent analysis and individual data are given in Table 2.

infusion. A notable feature of the pharmacokinetics of cisplatin in children is the variability in AUC achieved when the drug is administered on the basis of surface area (Table 2, Figure 2). The 2.7-fold variation in dose-normalised AUC seen in the present study is consistent with that observed by Bues-Charbit and associates in a smaller group of children [13]. To what extent this variability influences either the activity or toxicity of cisplatin in children is currently unknown; however, it prompts concern about the use of surface area-based dosing for cisplatin therapy in children. A recent analysis has shown that cisplatin dose rate, but not total dose, is a significant determinant of nephrotoxicity in children [19]. In adults, peak free and/or total cisplatin plasma concentrations, which will be determined by dose rate, are known to relate to renal side-effects [6–10]. Hence it is likely that cisplatin clearance will be an independent determinant of the efficacy of the drug in children.

Renal and hepatic function are two parameters that can influence interpatient pharmacokinetic variation; however, there was no relationship between GFR and the total plasma or renal clearances of free Pt in the children studied here. The total plasma-free Pt clearance exceeded GFR, whereas the mean ratio of renal clearance to GFR was not significantly different from unity. Studies in adults have shown that the renal clearance of cisplatin may involve both active renal secretion [10, 20, 21] and saturable tubular re-absorption [12, 22], as well as glomerular filtration. The results obtained here are consistent with one or more of these mechanisms operating in individual children. Overall, the urinary excretion of Pt following a 24 h infusion of cisplatin was 27% of the administered dose, a value which is again consistent with adult data [10, 23]. Given that renal excretion accounts for less than half of the cisplatin dose administered, the variability in plasma clearance observed must relate primarily to variation in the non-renal clearance of the drug. The non-renal clearance of cisplatin is thought to be largely due to tissue binding, as opposed to metabolism or biliary excretion; however, it is difficult to measure clearance due to tissue binding directly and, in the present study, there was no relationship between serum albumin and free Pt plasma clearance.

In the majority of children, total Pt concentrations following cisplatin exhibited a secondary peak during the elimination phase about 1–2 h after the end of the infusion (Figure 1(b)). This phenomenon has been observed in adult patients by Vermorken and associates [24] and in children by Dominici and associates [14]. The basis of the phenomenon may be ascribed to tissue absorption and release, or alternatively to enterohepatic recirculation [25]. The clinical importance of plasma protein-bound Pt is not fully understood. Early studies demonstrated convincingly that cisplatin is considerably less cytotoxic following reaction with serum protein and on the basis of these data the reaction of cisplatin with serum proteins is usually considered to be solely a detoxification pathway [26–28]. However, data from two recent cases of accidental cisplatin overdose suggest that bound Pt may retain toxic properties. In the first case, both emesis and loss of vision appeared to be temporally related to the levels of Pt in the plasma at time points where no intact cisplatin and little free Pt were likely to have been present [29], although only total Pt levels were actually measured. In the second case, plasma from a patient collected 22 days after cisplatin administration was found to be > 10-fold more cytotoxic in an *in vitro* assay than plasma from the same

Table 2. Pharmacokinetics of free Pt following cisplatin in children

	Non-compartmental analyses				Compartmental analyses				
Patient	AUC (mg/ml.min)/ (100 mg/m^2)	CL_{total} (ml/min/m^2)	CL_{total} (ml/min/kg)	CL_{renal} (ml/min/m^2)	CL_{total} (ml/min/m^2)	VD_{ss} (l/m^2)	$t_{1/2}$ (min)	Cp_{ss} (μg/ml)	K_e (min^{-1})
1	0.40	252	11	97	248	13.8	39	0.29	0.018
2	0.41	279	9	85	269	17.9	46	0.27	0.015
3	0.51	228	10	57	226	15.8	48	0.26	0.014
4	0.51	226	6	57	223	12.9	40	0.33	0.017
5	0.31	296	12	96	288	13.6	33	0.25	0.021
6	0.40	301	15	ND	ND	ND	ND	ND	ND
7	0.51	219	6	24	213	14.8	48	0.36	0.014
8	0.51	205	9	ND	224	17.0	53	0.25	0.013
9	0.63	175	8	35	174	8.6	34	0.33	0.020
10	0.81	123	5	26	152	11.0	51	0.43	0.014
11	0.30	278	9	ND	271	13.6	35	0.24	0.020
12	0.38	273	12	ND	270	12.3	32	0.20	0.022
13	0.67	137	5	28	157	10.0	44	0.47	0.016
14	0.40	249	7	73	245	13.5	38	0.28	0.018
15	0.38	271	9	ND	263	11.4	30	0.22	0.023
16	0.41	225	7	ND	197	10.0	35	0.57	0.012
17	0.50	217	9	ND	221	11.4	36	0.35	0.019
18	0.30	303	10	105	303	12.4	28	0.24	0.024
19	0.60	175	5	57	205	13.3	45	0.34	0.015
20	0.51	168	8	ND	166	9.2	39	0.42	0.018
21	0.38	302	12	ND	301	7.7	18	0.21	0.039
Mean	0.47	233	9	62	231	12.5	39	0.31	0.019
SD	0.13	55	3	29	46	2.7	9	0.09	0.006
Max	0.81	303	15	105	303	17.9	53	0.57	0.039
Min	0.30	123	5	24	152	7.7	18	0.20	0.012

patient collected prior to therapy [30]. In this latter study, although ultrafiltration demonstrated the presence of free Pt species at this time (ca. 10% of total Pt), it is unlikely that this represented intact cisplatin. Thus, the exact contribution of protein-bound Pt species to these clinical and *in vitro* toxicities has not been fully defined. Specifically, it is not clear whether bound Pt is toxic in its own right or if it acts as a reservoir for the formation of toxic ultrafiltrable Pt species other than cisplatin.

In resolving the importance of the secondary rise in total Pt concentrations, a comprehensive *in vivo* pharmacokinetic model would be valuable and Evans and associates have developed a first-order multicompartment operational model to simulate the disposition of cisplatin in children [31]. Simulations obtained with the model were accurate for parent cisplatin but were less so for total Pt serum concentrations. A modified pharmacokinetic model with a 'deep' peripheral compartment [32] in addition to the 'shallow' peripheral compartment [31] was proposed to explain the slow elimination of total Pt which becomes apparent when Pt concentrations are measured for longer periods. However, these models do not explain the complex elimination phase observed in the current study. The release of drug from a tissue compartment is the most likely explanation for the secondary total Pt peak as cisplatin does not, in an animal model [33], undergo significant biliary excretion and hence could not undergo enterohepatic recirculation.

The data for cisplatin given as a 24 h infusion show that steady-state concentrations ranging from 0.2 to 0.57 μg/ml were achieved shortly after the beginning of infusion, reflecting the rapid plasma clearance of the drug and that concentrations of free Pt did not exceed 0.6 μg/ml at any time. Cisplatin cytotoxicity *in vitro* is dependent on free drug exposure, i.e. the concentration time product ($C \times T$), regardless of whether concentration or time are altered [34]. The mean plasma free-drug AUC value observed in the patients studied here was 0.47 mg/ml.min/100 mg/m^2. Recently, Livingstone and associates [35] investigated the activity of cisplatin in seven human neuroblastoma cell lines. The cisplatin $C \times T$ required to produce 90% cell kill ranged from 0.13 mg/ml.min (7.5 μM×60 min) to 0.23 mg/ml.min (13 μM×60 min). These latter results show that currently used chemotherapeutic protocols achieve cisplatin AUC levels capable of causing significant levels of cytotoxicity in neuroblastoma cells *in vitro*.

In conclusion, the study described here shows that cisplatin pharmacokinetics in children are both quantitatively and qualitatively similar to those observed in adults. However, there was significant interpatient variability in free cisplatin exposure in children for a given surface area-based dose such that adaptive dosing may be necessary for the optimal use of this agent. The reasons for this variability are not known, although it is clear that cisplatin is subject to only limited urinary excretion in children and that other important and variable clearance pathways must operate.

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