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Cisplatin Disposition in Children and Adolescents with Cancer

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Summary. *The disposition of cisplatin was evaluated in 28 children and adolescents with cancer, as part of a phase II clinical trial. Patients received either 30 mg/m^2 (11) or 90 mg/m^2 (17) of cisplatin as a 6-h IV infusion. Serum samples and divided urine collections were obtained over 48 h following completion of the cisplatin infusion, and were assayed in duplicate for total platinum by atomic absorption spectrophotometry. Serum samples obtained up to 4 h after three cisplatin infusions were assayed for parent (free) cisplatin following ultrafiltration. The mean (± SE) elimination half-life of free cisplatin in serum was 1.3 (± 0.4) h. Serial serum concentrations of total platinum following 90 mg/m^2 dosages were adequately described by a biexponential equation. The mean (± SE) serum $T_{1/2}\alpha$ of total platinum was 0.42 (± 0.10) h and the mean (± SE) $T_{1/2}\beta$ was 44.43 (± 8.24) h. The intercompartment distribution rate constants of a two-compartment kinetic model indicate extensive tissue accumulation of total platinum, with a rate of transport into tissue compartments (K_{12}) that is about six times the rate of transport out of tissues (K_{21}). The mean (± SE) renal clearance of total platinum from 0–3 h was 37.36 (± 11.96) ml/min/m^2 and 35.8 (± 13.6) ml/min/m^2 for the 30 mg/m^2 and 90 mg/m^2 groups, respectively. This value decreased to 3.25 (± 0.94) and 2.16 (± 0.4) ml/min/m^2 for the two groups by the 6–12 h interval, and remained between 1 and 3 ml/min/m^2 for the duration of the observation period. The ratio of total platinum clearance to creatinine clearance decreased significantly ($P < 0.05$) beginning 3 h post-infusion. The change in renal clearance of total platinum is apparently a function of two independent first-order processes for renal clearance of parent drug and cisplatin metabolites.*

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Introduction

Cis-diamminedichloride platinum (CDDP, cisplatin) is an antineoplastic agent approved for the treatment of adult malignancies including metastatic testicular tumors and metastatic ovarian tumors [2]. Recent studies have also demonstrated its activity for neuroblastoma [10], osteosarcoma, and other pediatric malignancies [19].

Pharmacokinetic studies in adults have demonstrated that cisplatin disappears from serum in a biphasic manner, with a short initial half-life ($T_{1/2}$) of 23–49 min and a long secondary half-life of 14.4–73 h [4, 8, 9]. Because cisplatin has demonstrated activity in a number of pediatric malignancies, the present study was undertaken to assess the disposition of platinum in children and adolescents, in a manner similar to the earlier adult studies. Pharmacokinetic data were acquired as part of a phase II clinical trial in children with an established diagnosis of malignant solid tumor resistant to conventional agents.

Materials and Methods

Patient Selection. Patients were selected from those entered into the phase II clinical trial of cisplatin at St. Jude Children's Research Hospital. Requirements for entry into the study were a life expectancy of at least 6 weeks, measurable indicators of disease activity, adequate renal function (serum creatinine < 1.5 mg/dl, and blood urea nitrogen < 20 mg/dl), and informed parental consent.

Drug Administration and Patient Monitoring. Patients were randomized to receive cisplatin 30 mg/m^2 in a 6-h IV infusion every week, or cisplatin 90 mg/m^2 in a 6-h IV infusion every 3 weeks.

Intravenous hydration was initiated 2 h prior to administration of cisplatin, with mannitol 10 g/m^2 in dextrose 5% and NaCl 0.3% 500 ml/m^2. At the end of this infusion, furosemide 15 mg/m^2 was administered as an IV bolus, and this was immediately followed by

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the cisplatin dose mixed with mannitol 10 g/m^2 in dextrose 5% and NaCl 0.3%, 1,000 ml/m^2 by IV infusion over 6 h. The drug used in this study was provided by the National Cancer Institute.

Samples of 1–2 ml blood were collected and allowed to clot at the end of the cisplatin infusion (0 h) and $^1/_2$, 1, 4, 8, 24, and 48 h after completion of the infusion. The blood samples were centrifuged, and the serum was removed and frozen at −70° C until the platinum assay was performed.

In addition, serial serum or plasma samples obtained following selected cisplatin infusions were assayed for parent (non-protein-bound) platinum by a modification of the method of Bannister [1]. Samples were immediately separated and a volume of serum was placed in Centriflo Ultrafiltration cones (Amicon 2100, CF-50) and centrifuged for 10 min at 1,000 *g* (2,200 rpm) in a refrigerated centrifuge, to remove serum or plasma proteins. The ultrafiltrate was assayed for platinum by the procedure described below. Work done by LeRoy et al. [14] indicates that non-protein-bound platinum is virtually all unmetabolized parent cisplatin.

Urine was collected in timed interval specimens over 0–3, 3–6, 6–12, 12–18, 18–24, and 24–48 h following the cisplatin infusion. The volume of urine voided during each interval was determined and duplicate aliquots were frozen at −70° C for later analysis.

Platinum Assay. Duplicate quantitative analysis of the total platinum in each serum sample was performed by atomic absorption spectrophotometry with a Perkin-Elmer Model 403 Atomic Absorption Spectrophotometer by methods previously described [7]. Each sample was diluted 1 : 2 with a 1 : 1,000 solution of Triton X-100, and 50 µl of this diluted sample was analyzed for total platinum. Each sample was programmatically dried for 45 s at 125° C, charred for 45 s at 1,500° C, and atomized for 8 s at 2,700° C. Absorbance was read at 265.9 nm. The standard curve was prepared from data obtained with pooled human serum spiked with cisplatin in concentrations ranging from 125–10,000 ng/ml. The sample concentrations were then determined from a linear plot of the standard concentrations versus absorbance peak height. Urine samples were assayed for total platinum by an identical procedure, except that the standards were prepared in 0.1 N HCl.

Creatinine Assay. The creatinine concentration of each urine specimen was determined with the aid of a Kinetic Discrete Analyzer (KDA) instrument, manufactured by American Monitor.

Pharmacokinetic Calculations. Serial serum concentrations of total platinum were fit to the appropriate multiexponential equation by the NONLIN [17] least-squares computer program. The rate constants K_{12}, K_{21}, and K_e for a two-compartment model were calculated by the method of Loo and Riegelman [16] to correct for drug administration as a 6-h infusion and not as a bolus dose.

Renal clearance was calculated for each time interval according to the equation:

$$\text{clearance} = V \times Cu/Cp$$

where V is the urine flow rate in ml/min, Cu is the concentration of total platinum in the urine (µg/ml), and Cp is the serum concentration of total platinum at the midpoint of the collection interval (µg/ml).

Creatinine clearance for each time interval was calculated by dividing the rate (mg/min) of creatinine excretion (amount of creatinine excreted divided by length of collection interval) by the serum creatinine concentration.

Results

The pharmacokinetics of cisplatin was evaluated in 28 patients, 17 receiving 90 mg/m^2, and 11 receiving 30 mg/m^2. One patient was studied following six repeat doses, so that the disposition of cisplatin was evaluated following a total of 34 infusions. Nine patients had a diagnosis of neuroblastoma; five rhabdomyosarcoma; four osteosarcoma; five germ cell tumors; and five patients had other tumors. Nineteen were boys and nine were girls. The median age was 11.4 years, with a range of 1.7–20.5 years.

Eleven patients had a sufficient number of serum samples obtained (a minimum of five) to permit NONLIN fitting of serial concentrations of total platinum and subsequent multicompartment parameter estimations. Two of the patients received 30 mg/m^2 and nine received 90 mg/m^2. The semilogarithmic plot of serum concentrations versus time yielded a biphasic disposition curve, with a rapid initial decline in total platinum serum concentrations followed by a slower terminal disposition phase. The intercompartment distribution rate constants (K_{12}, K_{21}) and the overall elimination rate constant (K_e) of a two-compartment first-order kinetic model are summarized in Table 1. The mean (± SE) $T_{1/2}\alpha$ for the 90 mg/m^2 group was 0.42 (± 0.10) h and the mean (± SE) $T_{1/2}\beta$ was 44.43 (± 8.24) h. Mean platinum serum concentrations were proportionally lower following the 30 mg/m^2 infusions than following the 90 mg/m^2 dosage group. Similarly, the biphasic disposition curves were similar at the two dosage levels, and the mean rate constants for the two patients receiving 30 mg/m^2 were comparable to those determined in the 90 mg/m^2 dosage group.

Serial serum concentrations of parent (non-protein-bound) platinum were consistently lower than total platinum concentrations, and declined more rapidly. Serial serum concentrations measured at 0, $^1/_2$, 1, and 2 h following three infusions in two patients were assayed for cisplatin. The semilogarithmic plots of serum concentrations versus time were best

Table 1. Mean (± SE) two-compartment pharmacokinetic parameters following 90 mg cisplatin/mg^2 ($n = 9$)

α (h^{-1})	3.06	(± 0.85)
$T_{1/2}\alpha$ (h)	0.4158	(± 0.10)
β (h^{-1})	0.0224	(± 0.006)
$T_{1/2}\beta$ (h)	44.43	(± 8.24)
K_{12} (h^{-1})	2.274	(± 0.756)
K_{21} (h^{-1})	0.3570	(± 0.079)
K_e (h^{-1})	0.4529	(± 0.198)

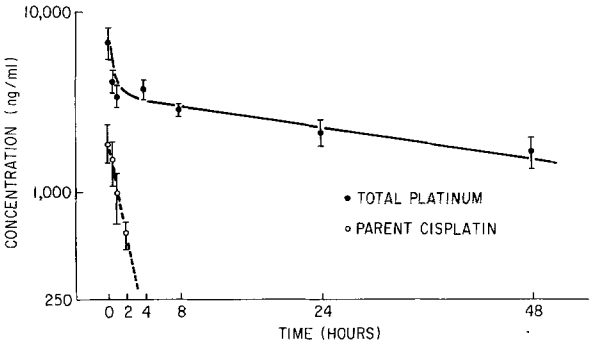

Fig. 1. Mean (± SE) total platinum (*solid line*) serum concentrations in 14 patients and mean (± SE) free cisplatin (*dashed line*) serum concentrations following three infusions in two patients who received cisplatin 90 mg/m^2 over 6 h

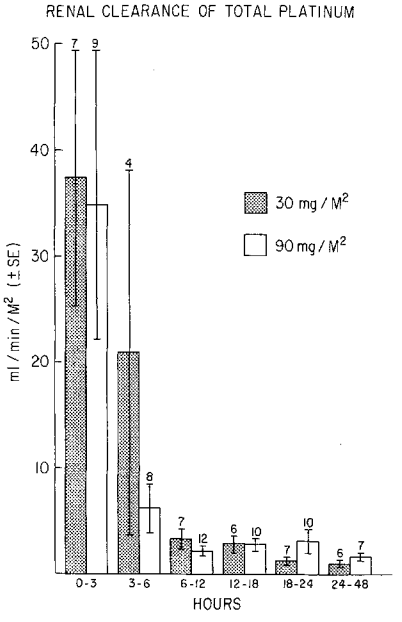

Fig. 2. Mean (± SE) renal clearance of total platinum in patients receiving 30 mg/m^2 (eight patients) or 90 mg/m^2 (12 doses in ten patients) of cisplatin as a 6-h infusion. Renal clearance is shown for six intervals following the end of the infusion

described by a monoexponential equation with a mean (± SE) half-life of 1.3 (± 0.4) h. As shown in Fig. 1, the concentrations of free cisplatin were five- to ten-fold lower than total platinum concentrations, and declined to unmeasurable levels within 4 h post-infusion.

Results of the renal clearance studies for 20 doses administered to 18 patients are shown in Table 2. The mean renal clearances, normalized for body surface area (m^2), are shown for each dosage group in Fig. 2. Eight of these patients received 30 mg/m^2 and ten received 90 mg/m^2. One of the patients in the 90 mg/m^2 group was studied after three doses. Renal clearance of total platinum in both groups was approximately 35 ml/min/m^2 at the end of the infusion, then declined to a relatively constant value of approximately 1–3 ml/min/m^2 beginning 6–12 h post-infusion.

The ratios of platinum clearance to creatinine clearance over each time interval are shown in Table 3. The one-way analysis of variance according to Duncan's New Multiple Range Test [5, 6] revealed that the mean 0–3 h interval clearance ratio was significantly different ($P < 0.05$) from the mean clearance ratios for all other time periods. There was no significant difference ($P = 0.05$) among the average clearance ratios for the other time periods.

Since children over a wide age range were studied, several parameters of the two-compartment model were correlated with age to detect age-related differences in these parameters. The constants $T_{1/2}\alpha$, $T_{1/2}\beta$, K_{12}, K_{21}, and K_e calculated for 11 courses which were fit to the two-compartment model were plotted versus age. The rate constant K_e had a significant correlation ($P < 0.05$) with age, as a larger value for K_e (more rapid elimination) was seen in older patients. The equation for the least-squares regression line was $y = 0.082x - 0.266$ ($r = 0.629$). However, the sample size is too small to yield conclusive results and the significance of this observation is unknown.

Table 2. Mean (± SE) renal clearance rates of total platinum

Interval (h)	30 mg/m^2 ($n = 8$) (ml/min/m^2)	90 mg/m^2 ($n = 12$) (ml/min/m^2)
0– 3	37.36 (± 11.96)	35.80 (± 13.6)
3– 6	20.92 (± 17.21)	6.2 (± 2.3)
6–12	3.25 (± 0.94)	2.16 (± 0.4)
12–18	2.94 (± 0.77)	2.85 (± 0.56)
18–24	1.23 (± 0.33)	3.14 (± 1.11)
24–48	1.02 (± 0.31)	1.69 (± 0.34)

Table 3. Mean (± SE) platinum/creatinine clearance ratios

Interval (h)	30 mg/m^2 ($n = 8$) (ml/min/m^2)	90 mg/m^2 ($n = 12$) (ml/min/m^2)
0– 3	0.391 (± 0.104)	0.937 (± 0.495)
3– 6	0.043 (± 0.034)	0.093 (± 0.023)
6–12	0.172 (± 0.110)	0.060 (± 0.011)
12–18	0.055 (± 0.013)	0.066 (± 0.011)
18–24	0.036 (± 0.014)	0.086 (± 0.039)
24–48	0.021 (± 0.010)	0.079 (± 0.023)

Discussion

A number of previous studies indicate that cisplatin is eliminated from serum in a biphasic manner, with an initial half-life of less than 1 h, and a slower terminal half-life of 1–3 days [3, 4, 7–9, 11–13, 15, 18, 20]. Previous studies also suggest that platinum may be detected in the body for several months after cisplatin administration [13, 18, 20].

In the earliest study, by DeConti et al. [4] the initial half-life was 25.0–49.0 min, which was followed by a slower half-life of 58.5–73.0 h. This study was carried out in ten adult patients who received ^{193}Pt-labeled cisplatin administered as an IV bolus dose over 1–5 min. There was no prehydration or diuresis, and the dosage ranged from 0.0661–3.15 mg/kg (about 2–95 mg/m^2).

In a recent study, Gormley et al. [9] examined the kinetics of cisplatin in eight adult patients receiving 70 mg drug/m^2, infused over 1 h. Patients received vigorous hydration and diuresis with furosemide and mannitol. The mean initial half-life of total platinum measured by atomic absorption spectrophotometry was 23 min and the mean terminal phase half-life was 67 h.

Frick et al. [8] studied total platinum kinetics following nine doses of cisplatin in seven patients. These patients received 100 mg/m^2 over 2 h, with hydration both preceding and following the cisplatin and diuresis with mannitol. These authors observed a mean initial half-life ($T_{1/2}\alpha$) of 76 min (range: 37.8–103.8 min) and a mean terminal ($T_{1/2}\beta$) half-life of 26.8 h (range: 14.4–57.7 h), determined from the urinary excretion rate of platinum assayed by atomic absorption spectrophotometry. These authors suggested that the more rapid terminal excretion they had observed than in previous studies may have been related to the pre- and posthydration and mannitol diuresis. However, urinary excretion of platinum was measured for only 24 h after drug administration, and this may explain their shorter terminal half-life.

Data from the present study indicate that the pharmacokinetics of total platinum is similar in children and adults. The mean $T_{1/2}\alpha$ (0.46 h) and $T_{1/2}\beta$ (42.2 h) are within the range of values reported in previous adult studies [4, 8, 11]. In addition, our data indicate that the concentrations of parent (free) cisplatin are lower than simultaneous serum concentrations of total platinum, and that parent cisplatin disappears from the serum with a short half-life of 1.3 h. Serum concentrations of parent cisplatin were undetectable after 4 h post-infusion, although relatively high concentrations of total platinum persisted throughout the observation period.

These data also suggest a tendency for tissue accumulation of total platinum, as indicated by a mean rate constant for transport into the tissue compartment (K_{12}) that is about six times faster than the rate constant for transport out of tissue (K_{21}). This is consistent with the observation of Gormley et al. [9] that serum concentrations of total platinum were detectable 21 days after a dose of platinum and were about 20 times greater than predicted on the basis of the $T_{1/2}\beta$ determined in that study.

The renal clearance of total platinum decreased markedly over the 48-h observation period. Two possible mechanisms for this observation are suggested: (1) a change in renal function, altering the ability of the kidney to excrete platinum in the urine; or (2) a change in the platinum species (i.e., metabolism), altering its renal excretion. The ratio of platinum clearance to creatinine clearance was significantly higher over the 0–3 h interval than in any other observation period, which suggests that renal function (as measured by creatinine clearance) did not change and that the observed changes in renal clearance of platinum were not due to decreased renal function. Therefore, the second mechanism for the change in renal clearance of platinum appears to provide a better explanation for these observations, and the pharmacokinetic basis for this explanation has been established in a companion paper (W. E. Evans et al. 1981, unpublished work).

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