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Constancy in Integrated Cisplatin Plasma Concentrations Among Pediatric Patients

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Keywords: Cisplatin; carboplatin; pharmacokinetics; drug modeling

The authors report on the variability in the integrated quantity of free (unbound) plasma cisplatin (area under curve of plasma concentration versus time, AUC). The AUC was measured in 19 patients receiving cisplatin doses proportional to body surface areas (BSA), 30mg/m2 over 1 hour. The relative standard deviation (RSD, population standard deviation divided by mean value) for the maximum free plasma cisplatin concentration (C_{max}, μM) was 0.338; for the half-life ($t\frac{1}{2}$, minute), 0.210; and for the AUC (μM minute), 0.320. Thus, BSA-based dosing gave significant variability in the AUC. We attempted to use $(weight)^a(height)^b$, seeking values of a and b that gave the smallest RSD in AUC, but only minimal improvement could be obtained by deviating from the BSA formula (a = b = 0.5). However, dosing proportional to $(weight)^d(C_{max})^f$ (with d ≈ 3/4 and f ≈ –1) reduced the RSD in AUC from ~1/3 to ~1/10. Dosing proportional to $(weight)^m(C_{max})^n(t_{1/2})^p$ (with m≈ 0.7, n ≈ –1, and p ≈ –½) reduced it further, to ~1/32. In contrast, using $(weight)^d(C_{max})^f(age)^g$ gave no improvement over $(weight)^d(C_{max})^f$. The authors conclude that the inconsistency in AUC can be reduced 10-fold with dosing proportional to the weight and the drug pharmacokinetic parameters $[(weight^{0.7}) (C_{max} t_{1/2}{}^{0.5})]$.

Variability in the integrated quantity of free plasma cisplatin, typically measured as area under a curve of plasma concentration versus time (AUC), is a significant clinical problem.[1-6] Peng et al, for example, stated, "BSA-based dosing of cisplatin in children is not satisfactory." [4(p1823)] Similarly, a pediatric formula for carboplatin dosing that involves glomerular filtration rate is currently receiving attention[7-11] However, a solution to the inconstancy problem for cisplatin (an approach that assures desired AUC for all patients) is lacking. Reducing this inconstancy assures effective treatment for all patients and minimizes the toxicity.

We evaluate here the variability of free (unbound) plasma cisplatin pharmacokinetics in 19 patients who participated in the phase I trial 9970 within the Children Oncology Group.[6] Cisplatin was administered intravenously in combination with irinotecan. The cisplatin dose was proportional to body surface area (BSA), 30 mg/m^2. Values of AUC were calculated from plasmameasurements taken after drug administration. The variability, calculated as the ratio of population SD in AUC to mean AUC, was ~1/3, unacceptably high. We investigated the effect of other dosing formulas based on patient parameters. Using the results of this investigation, we developed a formula for cisplatin dosing that resulted in much more constant AUC (smaller variability).

Materials and Methods

Materials

Platinum (Pt) atomic spectroscopy standard (H_2PtCl_6, 1 mg/mL in 10% hydrochloride) was purchased from PerkinElmer (Norwalk, Conn), nitric acid Ultrex II ultrapure reagent was purchased from J. T. Baker (Phillipsburg, NJ), and Amicon Centrifree micropartition unit (30 000 M_r cutoff, catalog #4104) was purchased from Millipore (Billerica, Mass).**[End of page 443]**

Patients

Nineteen patients (7 female patients and 12 male patients) received 1-hour intravenous infusion of cisplatin at 30 mg/m^2. All patients had normal serum creatinine and glomerular filtration rate for age and normal serum albumin ≥2.5 g/dL. Body surface area was determined as [square root of height (cm) × weight (kg)] ÷ 60. Blood samples (1 mL each) for plasma cisplatin determinations were drawn from central lines into EDTA tubes before cisplatin

infusion and then at 0, 15, 30, 45, 60, and 90 minutes from the end of cisplatin infusion. The samples were centrifuged immediately at 4°C, and an aliquot of the plasma was centrifuged in the Amicon Centrifree micropartition unit in a fixed-angle rotor (4°C, 2000g) for 1 hour. The ultrafiltrates were stored at –20°C, shipped on dry ice, and analyzed for cisplatin content immediately on arrival using atomic absorption spectroscopy.[6] A more complete description of the study design, treatment, and assay validation has been reported previously.[6]

The participating sites were phase I institutions within the Children Oncology Group. The study was approved by the institutional review board of the participating institutions. Written informed consent was obtained for each patient before they entered the study.

Platinum Analysis

Platinum analysis was done on the graphite furnace of a Shimadzu atomic absorption spectrometer. The instrument was supplied with a hollow cathode Pt lamp, deuterium arc background correction, and graphite tubes. Argon gas and tap water flowed through the furnace. The Pt standard (H_2PtC_{l6}) was a 51.3 nM (0.01 mg/L) solution, freshly prepared by serial dilutions of the Pt atomic spectroscopy standard stock in dH_2O plus1% HNO_3 (volume to volume). A calibration curve was generated immediately before each measurement. It was linear from 0 to 1.0 pmol ($r \geq .99$); the lower limit of detection was ~0.1 pmol. Each sample was measured in triplicate. The injection volume was 20 μL. The furnace program was drying at 70°C for 10 seconds, drying at 90°C for 10 seconds, drying at 120°C for 10 seconds, charring at 250°C for 10 seconds, charring at 800°C for 25 seconds, charring at 30°C for 20 seconds, atomizing at 2600°C for 5 seconds, and burn off at 3000°C for 3 seconds. Calculations were based on the molecular weight of Pt of 195.078.

Data Analysis

The AUC was calculated for each patient from the values of the maximum concentration (C_{max}, plasma concentration at the end of cisplatin infusion, μM) and k (decay constant obtained by fitting measured plasma concentrations to Ae^{-kt}, minute^{-1}). Details of the calculation are given below. The relative standard deviation (RSD) was determined as population SD of AUC divided by mean AUC. The smallness of RSD is a measure of constancy.

To estimate AUC for dosing schemes other than BSA, the AUC for each patient was assumed proportional to the administered dose, that is, AUC for dose D_1 is calculated as AUC for dose D_2 multiplied by D_1/D_2. This assumption is exact for linear kinetics for all values of D[10,13]; it approaches exactness in general when D^1 is close to D^2 because it represents the leading term in a power-series expansion of AUC as a function of D. The assumption of proportionality enabled us to estimate AUC for any dosing scheme from the AUC measured for BSA-based dosing. We then investigated combinations of patients' parameters that would make AUC as constant as possible (give smallest RSD).

The AUC was calculated as a sum of 2 parts, $C^{(1)}$ and $C^{(2)}$. The contribution for time (t) greater than 60 minutes, $C_{(2)}$, was calculated from C_{max} and half-life ($t_{1/2}$), assuming free plasma of the molar concentration of cisplatin ([cisplatin]) decayed exponentially with a decay constant $k = \ln(2)/t_{1/2}$:

$$C^{(2)} = \int_{60}^{\infty} C dt = \int_{60}^{\infty} C_{max} e^{-k(t-60)} dt = C_{max}/k = C_{max} t_{1/2}/\ln 2.$$

The exponential decay was verified from the measured plasma concentrations. The contribution for t < 60 minutes, $C^{(1)}$, cannot be calculated exactly because no measurements of free plasma [cisplatin] were made during drug infusion. Lower and upper bounds on $C^{(1)}$ can be obtained assuming free plasma [cisplatin] rises linearly with t until it reaches the steady-state value C_{max}. The lower bound on $C^{(1)}$ with this assumption, corresponding to free plasma [cisplatin] = $C_{max} \times (t \div 60)$ is $C^{(1)} = C_{max} \times 30$ minutes. The upper bound, assuming a fast rise in C, so free plasma [cisplatin] $\approx C_{max}$ for t ≤ 60 minutes, is $C^{(1)} = C_{max} \times 60$ minutes. The actual value of $C^{(1)}$ for slow infusion should be between these 2 values. 12 The high and low AUC values were calculated by adding $C_{max} t_{1/2}/\ln 2$ to either $C_{max} \times 60$ or $C_{max} \times 30$, and **[End of page 444]**

Table I Patients' Parameters and Measured Free Plasma Cisplatin Pharmacokinetic Values

| | | Patients | | | | | | BSA Dosing | |
| | | | | | | | | Low AUC, | High AUC, |
Patient #	Gender	Age, y	Height, cm	Weight, kg	BSA, m^2	C_{max} (µM)	$t_{1/2}$ (min)	µM min	µM min
1	F	15	149.0	44.3	1.354	5.8	27	400	574
2	F	6	164.0	51.0	1.524	3.2	25	211	307
3	F	11	155.0	55.2	1.542	4.5	23	284	419
4	F	15	101.4	17.6	0.704	6.3	21	380	569
5	F	9	157.0	54.9	1.547	5.6	23	354	522
6	F	15	131.3	26.8	0.989	6.6	21	398	596
7	F	5	176.0	44.3	1.472	3.3	24	213	312
8	M	20	109.0	19.0	0.758	5.0	43	460	610
9	M	4	138.0	37.0	1.191	4.5	22	278	413
10	M	18	137.0	36.2	1.174	3.8	24	246	360
11	M	4	110.0	17.8	0.737	3.1	28	218	311
12	M	19	178.3	53.2	1.623	8.4	20	494	746
13	M	14	101.0	17.0	0.691	3.6	30	264	372
14	M	16	173.5	48.9	1.535	4.5	21	271	406
15	M	22	162.5	42.5	1.385	2.0	21	121	181
16	M	17	165.2	66.4	1.746	5.1	24	330	483
17	M	10	181.0	58.0	1.708	4.1	33	318	441
18	M	4	168.9	79.0	1.925	4.5	25	297	432
19	M	14	113.0	21.0	0.812	2.2	28	155	220
Range		4-22	101-181	17-79	0.69-1.9	2.0-8.4	20-43	121-494	181-746
Median		14.0	152	43.4	1.38	4.5	24.0	284	419
Mean		12.5	143.6	40.4	1.28	4.53	25.42	300	435
SD		5.8	28.7	18.4	0.385	1.53	5.33	95.8	139.4
Relative SD		0.464	0.200	0.455	0.300	0.338	0.210	0.320	0.320

Two assumptions were made in calculating the area under a curve of plasma concentration versus time (AUC) (see Methods). C_{max}, maximum concentration; $t_{1/2}$, half-life; BSA, body surface area; AUC, area under a curve of plasma concentration versus time.

calculations were made with both assumptions. Conclusions drawn from the 2 sets of AUC values were very similar.

Results

In each patient, the drug decay was monoexponential. Table I shows the measured values of C_{max} and $t_{1/2}$ for the 19 patients for BSA-based dosing and calculated high and low values of AUC. For all patients, C_{max} for free plasma cisplatin was [mean ± SD (n)] 4.7 ± 1.6 (19) µM and $t_{1/2}$ was 25.4 ± 5.4 (19) minutes. The RSD in AUC (high or low) for all patients was 0.320.

We then searched for an optimal usage of patients' weight (Wt) and height (Ht) to determine dosing. Dosing was set proportional to (weight)^a(height)^b and the predicted AUC was calculated as (AUC from BSA based dosing) ÷ [(weight)$^{1/2}$(height)$^{1/2}$] × [(weight)^a (height)^b]. The optimal values of the exponents a and b were determined by minimizing RSD for the predicted AUCs. The results of these calculations are shown in Table II (optimal Ht/Wt dosing). For the high AUC, the optimal values of a and b were 0.61 and 0.19, respectively (giving RSD = 0.319). For the low AUC, the optimal values of a and b were 0.60 and 0.31, respectively (giving RSD = 0.319).

The RSD of 0.319 is essentially the same as that obtained using BSA, that is, $a = b = 0.5$ (Table I). This finding is not surprising because height and weight are correlated, and thus only the sum of the exponents is of importance. To show this, we calculated the AUC for dosing proportional to (weight)^c(height)$^{1-c}$. The RSD is**[End of page 445]**

Table II Calculated Area Under a Curve of Plasma Concentration Versus Time (AUC), in µM min, for 3 Dosing Schemes

Patient #	Optimal Ht/Wt Dosing		Wt/C_{max} Dosing		Wt/C_{max}/$t_{\frac{1}{2}}$ Dosing	
	Low	High	Low	High	Low	High
1	226.51	191.81	311.34	445.66	296.82	430.12
2	119.01	101.24	296.27	428.65	295.84	429.40
3	163.24	141.86	297.71	435.38	308.14	446.90
4	210.76	192.42	253.62	389.79	306.39	444.21
5	202.86	175.93	295.64	432.00	304.72	441.55
6	219.33	195.43	251.03	380.79	291.30	422.22
7	116.84	99.08	268.79	393.21	278.58	404.29
8	253.60	203.55	381.97	518.92	298.12	432.30
9	156.83	138.40	275.61	410.95	304.21	441.05
10	138.66	120.60	288.26	423.82	303.52	440.04
11	119.18	102.72	285.99	419.24	294.31	427.29
12	275.41	240.96	255.24	382.01	284.71	412.37
13	146.01	125.45	306.57	444.40	302.89	439.37
14	150.57	130.97	259.48	386.79	287.03	416.29
15	67.11	58.62	259.85	389.10	296.33	429.70
16	190.95	163.80	311.45	449.14	307.95	446.13
17	178.34	143.20	343.56	471.64	284.92	412.94
18	174.20	148.44	330.46	471.17	314.47	455.92
19	85.74	73.45	296.61	430.69	302.79	437.56
Range	67-141	59-118	251-382	351-519	279 - 314	404 - 456
Median	163.24	141.86	295.64	428.65	298.12	432.30
Mean	168.17	144.63	293.13	426.49	298.06	432.09
SD	53.69	46.21	33.02	35.32	9.22	13.30
Relative SD	0.319	0.319	0.113	0.083	0.0309	0.0308

The AUC for each patient is assumed proportional to the dose (see Methods). C_{max}, maximum concentration; $t_{\frac{1}{2}}$, half-life.

plotted versus c in Figure 1. Varying c between 0.1 and 0.9 increased RSD by less than 10% from BSA dosing (c = 0.5).Therefore, not much was gained by dosing proportional to the geometric mean of height and weight (BSA) rather than by either height, weight, or $(weight)^c (height)^{1-c}$ with $0 < c < 1$.

The above results suggested patients' parameters other than height and weight must be taken into account to improve constancy in AUC. These parameters might include rates of drug elimination, distribution, and biotransformation, which were reflected in the measured C_{max} and $t_{\frac{1}{2}}$. Because the RSD in C_{max} was greater than that in $t_{\frac{1}{2}}$ and because the RSD in weight was greater than that in height (Table I), we considered dosing proportional to $(weight)^d \times (C_{max})^f$. The predicted values of AUC were calculated by dividing the values of AUC in Table I by (BSA/ BSA) and multiplying them by $(weight/ weight)^d$ and by $(C_{max}/(C_{max}))^f$, where brackets indicate mean values. The mean values were incorporated in the formula so that predicted AUC would be the same size as those of Table I. We then sought the values of d and f, which gave the smallest calculated RSD in AUC.

The results (Table II) demonstrated a great improvement in constancy over BSA-based dosing. The best values of d and f were 0.78 and –1.01 for the low AUC results and 0.75 and –1.01 for the high AUC results. (The inverse proportionality to C_{max} is not surprising, given that calculated AUC is proportional to C_{max}, but simply dosing inversely to C_{max} cannot achieve constancy in AUC.) The RSD was reduced to 0.113 and 0.083, respectively. Thus, dosing proportional to $(weight)^{3/4}/C_{max}$ reduced the RSD to ~1/10, 3 times lower than the value obtained with BSA dosing.

One can lower the RSD even further by dosing proportional to powers of 3 patients' parameters, that is, $(Wt)^m (Cmax)^n (t_{\frac{1}{2}})^p$. We calculated the resultant AUC according to the following: **[End of page 446]**
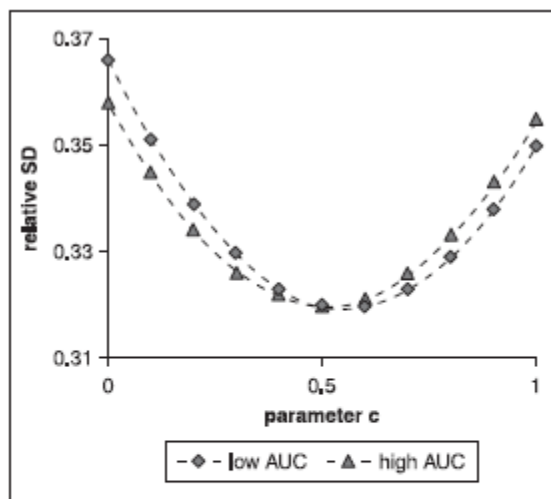
Figure 1. Relative standard deviation in high and low area under a curve of plasma concentration versus time (AUC), calculated assuming dosing proportional to $(weight)^{c}(height)^{1-c}$, as a function of c. Relative standard deviation varies by less than 10% for $0.1 < c < 0.9$.

$$AUC = (AUC)_{BSA} \frac{\langle BSA \rangle}{BSA} \left(\frac{Wt}{\langle Wt \rangle} \right)^{n} \left(\frac{C_{max}}{\langle C_{max} \rangle} \right)^{n} \left(\frac{t_{1/2}}{\langle t_{1/2} \rangle} \right)^{p}$$

and optimized by minimizing RSD with respect to m, n, and p. For low AUC, the optimum values of the exponents were m= 0.69, n = –1.03, p = –0.61; the RSD was only 0.031. For high AUC, the optimum values of the exponents were almost the same: m= 0.69, n = –1.03, p = –0.44; the RSD was again 0.031. Thus, a lowering in RSD by another factor of 3 was achieved.

To investigate whether this substantial lowering was simply a consequence of using 3 rather than 2 parameters, we considered dosing proportional to $(weight)^{m}(age)^{n}(C_{max})^{p}$. For low AUC, the results were m = 0.78, n = –0.003, p = –1.00 (RSD = 0.113). For high AUC, the results were m = 0.75, n = 0.002, p = –1.01 (RSD = 0.083). Because the exponent of age was essentially zero (so the other exponents had the values they did in the 2-parameter dosing formula), taking patients' age into account presented no advantage.

Discussion

It is clear that BSA dosing is associated with significant variability in AUC (RSD ~ 1/3) (Table I). In our calculations, we use a few parameters (height, weight, age, C_{max}, and $t_{1/2}$) to construct a cisplatin dosing formula that gives more constant AUC. Insignificant lowering of RSD in AUC, relative to BSA dosing, was obtained using patients' height and weight only. The reason for the variability in AUC resulting from BSA dosing thus appears to be related to variables other than height and weight, such as rates of drug elimination, distribution, and biotransformation.[12-14] None of these parameters is currently evaluated in patients receiving cisplatin. However, C_{max} (plasma drug concentration at the end of infusion) is measured and reflects these parameters.

Our calculations show RSD in AUC can be reduced from ~1/3 (for BSA dosing) to ~1/10 if dosing is proportional to $(weight)^{3/4}/C_{max}$. They suggest that a further reduction by a factor of 3 in RSD can be achieved by dosing proportional to powers of 3 parameters: weight, C_{max}, and $t_{1/2}$. On the other hand, dosing proportional to powers of weight, C_{max}, and age gives no improvement over dosing proportional only to powers of the first 2 variables. This finding confirms the source of the variation in AUC is kinetics, and parameters such as C_{max} and $t_{1/2}$ should be taken into account to produce constancy. The former is more easily obtained because it requires only a single measurement, whereas $t_{1/2}$ requires a series of measurements.

As an example of use of the 3-parameter dosing formula, suppose our target value of AUC is 367.5, which is the mean value of the low and high AUCs for all patients, ½(435 + 300) (Table I). To establish the constant of proportionality in the dosing formula,we divide the AUC for each patient (Table I) by [30 mg/m² × BSA (in m²)] and multiply by [(Wt0.7)(Cmax –1)(t½ –½)], giving new AUCs with a mean value of 5.619. Because our target value is 367.5, we multiply all doses by 367.5/5.619 = 65.4. Our calculations predict that if the administered

cisplatin doses were $(65.4) \times [(W^{t0.7})(C_{max}^{-1})(t_{1/2}^{-1/2})]$, the mean AUC would be 367.5, and the population SD would be 11.99, making the RSD 0.0326. Based on the formula, patient 1 (Table I) would receive a cisplatin dose of $65.4(44.3)^{0.7} \div (5.8 \times 27^{1/2}) = 30.8$ mg instead of 40.6 mg = (30 mg/m^2)(1.354 m^2). In contrast, patient 2 would receive a cisplatin dose of $65.4(51.0)^{0.7} \div (3.2 \times 25^{1/2}) = 64.1$ mg instead of 45.7 mg = (30 mg/m^2)(1.524 m^2). All our calculations are based on the approximation that changing a patient's dose from D_1 to D_2 will change the patient's AUC from A_1 to $(D_2/D_1)A_1$; this approximation approaches exactness when D_2/D_1 approaches unity.

Our aim in this work was to find a dosing formula, based on easily measurable patients' parameters, which would reduce the variability in delivered AUC from the present high level (RSD ~1/3 using BSA, dosing proportional to (Ht × Wt)$^{1/2}$). Using powers of height and weight only, one can get only minimal improve- **[End of page 477]** ment, but RSD can be reduced by a factor of 3 with dosing proportional to $(Wt)^{3/4}/C_{max}$. Another factor of 3 improvement in RSD is possible for dosing proportional to $[(Wt_{0.7})(C_{max\ -1})(t_{1/2\ -1/2})]$, but the measurement of $t_{1/2}$ is more complicated than the measurement of C_{max}. The proposed method for cisplatin dosing requires clinical validation by future studies. Nevertheless, the data show that pharmacokinetics variables (C_{max} and $t_{1/2}$) contribute importantly to cisplatin AUC variations. Thus, limited pharmacokinetics samples may be necessary, especially during high-dose cisplatin treatment or when treating young infants. For example, when high-dose cisplatin is given (ie, 20-40 mg/m$_2$/day · 5 consecutive days), limited pharmacokinetics samples could be collected on day 1 to guide the dosing on days 2 through 5.

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