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Pharmacokinetic Comparison of Cisplatin in Solution w Common Lyophilized Cisplatinum (Platinol)

*J. B. Vermorken, *W. J. F. van der Vijgh, *I. Klein, *H. E. Gall, †T. A. W. Splin ‡A. A. M. Hart, and *H. M. Pinedo

**Department of Oncology, Free University Hospital, ‡Netherlands Cancer Institute, Amsterdam, and †Departn Internal Medicine, Dijkzigt Hospital, Rotterdam, The Netherlands*

Summary: Total platinum kinetics were studied after the administration of two formulation products of cisplatin: the lyophilized form and a ready-to-use solution. Twelve patients received both preparations during two successive cycles in a randomized crossover study. Platinum concentrations in plasma and urine were measured by atomic absorption spectrometry. Data were analyzed by means of a mixed-effect analysis of variance. Areas under the concentration–time curves up to 96 h were increased ($p = 0.026$) and slopes of the elimination phase were decreased ($p = 0.035$) during cycle 2 when compared with cycle 1. However, no difference in these two parameters was observed when comparing the two formulations. Three-day urinary platinum excretion was not related to either the treatment cycle or the formulation used. Because of its convenience of use and reduced risk of aerosolization, the ready-to-use formulation seems preferable. Key Words: Cisplatin—Ready-to-use solution—Total platinum pharmacokinetics.

Cis-diamminedichloroplatinum II (cisplatin) was the first of the platinum coordination complexes to be used as an anticancer agent in humans. It proved to be an important addition to the antineoplastic armamentarium, with a broad therapeutic spectrum (1). Although the exact mechanism of action is still uncertain, cisplatin appears to exert its cytotoxic effects by the ability to bind to DNA (2). Cisplatin is commonly administered intravenously, either by bolus injection or by prolonged infusions, every 3–4 weeks. The usual dosage ranges from 50 to 120 mg/m^2 body surface area, which is given either as a single dose or in divided doses over 5 days. Alternative routes, such as intraarterial and intracavitary administration, are being increasingly investigated in order to improve the therapeutic index (3, the past, dose-limiting toxicity consisted of damage. However, by applying an intensive venous hydration program with concomitant f diuresis, this can now be successfully circumv (5). Hydration and diuretics do not seem to any impact on other adverse effects such as n and vomiting, neurotoxicity, ototoxicity, an elosuppression, nor do they seem to alter the macokinetics of the drug (6–8).

In the past we have studied the pharmacoki of cisplatin after different intravenous admir tion schedules, using cisplatin in its original l lized formulation (9–12). Recently, a ready-t solution of cisplatin (Platinol) has become able, providing major advantages in clinical tice. However, no data on its pharmacoki have been available. We therefore perforn crossover comparative study of the pharma netics of the old and new formulations.

Address correspondence and reprint requests to Dr. J. B. Vermorken at Department of Oncology, Free University Hospital, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.

MATERIALS AND METHODS

Patients

Twelve patients, four men and eight women, with a median age of 50 years (range 46–75 years) participated in the study. All patients had normal renal function. Only two had received cisplatin at an earlier stage. Their diagnoses were head and neck cancer (five), ovarian cancer (five), small cell lung cancer (one), and non–small cell lung cancer (one). Cisplatin was administered either as single drug (seven patients) or in combination with other cytostatic drugs. All patients received at least two courses of cisplatin at the same dosage, using similar methods of administration.

Cisplatin Solutions

The lyophilized formulation (Bristol Myers, Bussum, The Netherlands) was reconstituted with sterile water. The resulting solution contained, per milliliter, cisplatin (1 mg), sodium chloride (9 mg), and mannitol (10 mg). The pH of the solution was 2–3. This solution was further diluted with normal saline to obtain a cisplatin concentration of 0.5 mg/ml in order to make it comparable with the ready-to-use solution (Bristol Myers). This was delivered in 50-ml ampules containing, per milliliter, cisplatin (0.5 mg), sodium chloride (9 mg), and hydrochloric acid to adjust the pH to 2–3.

Study Design

Patients received the lyophilized formulation or the ready-to-use solution in the first treatment cycle at random. For the second course all patients crossed over to the alternative formulation. The drugs were used immediately after preparation. At each course the drug was administered by infusion pump. Standardized pre- and posthydration schemes were used as described earlier (9). Dosage, duration of infusion, and route of administration are specified in Table 1.

Blood samples were drawn in heparinized tubes prior to administration, at the end of infusion, and 5, 10, 30, 60, 120, 300, 1,260, and 1,440 min thereafter. Blood sampling then was continued daily, at 24-h intervals, for ≥4 days. Additional samples were obtained after the start of 3-h infusions (60, 120 min) and 6-h infusions (60, 120, 240 min). All samples were centrifuged, and plasma was removed. If possible, urine was collected for ≥3 days after administration of cisplatin. All plasma and urine samples were stored at −30°C until analysis.

Platinum Analysis

All samples were thawed just before analysis and diluted (1:1 vol/vol for plasma and 9:1 vol/vol for urine) with a solution containing 0.15 *M* NaCl in 0.4 N HCl for plasma and 0.6 *M* NaCl in 2N HCl for urine. The concentration of platinum in all samples was determined by flameless atomic absorption spectrometry using a Perkin Elmer atomic absorption spectrophotometer model 5000. A four-stage heating program was used, consisting of drying at 110°C for 65 s, ashing at 1,400°C for 55 s, atomization at 2,650°C for 3 s, and conditioning at 2,550°C for 5 s.

Data Analysis

Areas under the plasma concentration–time curves (AUCs) were calculated by the trapezoidal rule from the start of the infusion to 96 h. The AUCs were corrected for differences in total sampling time (AUC_{96-t}). Also, the AUCs of the second course and the AUC of patient 6 during the first course were corrected for the initial platinum concentration in plasma ($AUC_{res\ 0-96}$) Thus:

$$AUC_{0-96} = AUC_{0-t} - AUC_{96-t} - AUC_{res\ 0-96}$$

in which

$$AUC_{0-t} = \sum_{i=0}^{n-1} \frac{(C_i + C_{i+1})}{2} (t_{i+1} - t_i)$$

$$AUC_{96-t} = \frac{B}{\beta} \cdot e^{-96\beta}[1 - e^{-\beta(t-96)}]$$

$$AUC_{res\ 0-96} = \frac{C_0}{\beta_1}[1 - e^{-96\beta_1}]$$

and t is the time during and after the end of the infusion (h), β is the elimination slope over days 1–4 (h^{-1}), β_1 is the elimination slope of the first cycle (h^{-1}), B is the intercept of the back extrapolated elimination phase with the ordinate (μg/ml), and C_0 is the initial platinum concentration (μg/ml).

Elimination slopes were calculated over the time interval days 1–4 by linear least-squares analysis. In addition, concentration–time curves were analyzed by curve-fitting with the nonlinear least-

TABLE 1. *Basic data of cisplatin administration and pharmacokinetics*

Patient no.	Cycle no.	S/P	Infusion	Dose (mg/m²)	Infusion time (min)	Starting concentration (μg/ml)	B (μg/ml)	β (min⁻¹)	Cumulative 3-day urinary excretion (% of dose)
1	1	S	i.v.	100	37	0.00	2.61	0.0001358	37.8
	2	P			37	0.33	2.95	0.0000955	39.6
2	1	P	i.v.	100	15	0.00[a]	2.50	0.0001301	33.9
	2	S			15	0.31	3.85	0.0001309	25.8
3	1	P	i.v.	75	30	0.00	1.10	0.0000099	48.4
	2	S			55	0.16	1.55	0.0000442	23.1
4	1	S	i.v.	75	30	0.00	1.29	0.0000996	31.5
	2	P			30	0.18	1.72	0.0000726	24.2
5	1	P	i.v.	50	35	0.00	1.52	0.0001238[b]	—
	2	S			60	0.22	1.88	0.0001003[b]	31.2
6	1	P	i.v.	75	30	0.19[a]	2.27	0.0000989	—
	2	S			30	0.35	2.34	0.0000639	13.0
7	1	S	i.v.	50	60	0.00	1.36	0.0001048	32.5
	2	P			90	0.25	1.52	0.0000703	33.7
8	1	P	i.a.	98	365	0.00	2.18	0.0000902	21.7
	2	S		91	368	0.45	2.36	0.0000455	31.1
9	1	S	i.v.	60	30	0.00	1.33	0.0000429	32.2
	2	P			30	0.29	1.67	0.0000415	38.4
10	1	P	i.a.	64	364	0.00	1.72	0.0000910	38.2
	2	S		69	357	0.36	2.00	0.0000866	33.5
11	1	P	i.v.	100	159	0.00	2.52	0.0001102	21.3
	2	S			169	0.37	2.63	0.0000568	—
12	1	P	i.v.	75	188	0.00	1.99	0.0001572	—
	2	S			178	0.23	2.37	0.0001078	—

S, ready-to-use solution; P, reconstituted powdered lyophilized formulation; B, intercept of the back extrapolated elimination phase with the ordinate; β, elimination slope over days 1–4; i.v., intravenous; i.a., intraarterial.

[a] Patients who received prior cisplatin treatment.

[b] Slope calculated over days 2–5.

squares analysis (NLIN) method of Marquardt (13). Data were analyzed by means of a mixed-effect analysis of variance.

RESULTS

Four patients received the ready-to-use solution during the first treatment cycle, while the other eight patients started on the lyophilized formulation. Basic pharmacokinetic parameters are summarized in Table 1, and both the corrected AUCs and the normalized AUCs (AUC/dose/m²) are tabulated in Table 2. It is evident from both tables that changes in pharmacokinetic parameters do occur between both cycles. In particular, this concerns changes in the elimination slopes and the AUCs. It should be emphasized that the kidney function hardly changed during the observation period. With respect to serum creatinine level, only one patient (no. 2) showed an increase in serum creatinine of 0.3 mg/100 ml (and concomitantly a decrease in creatinine clearance of 26%), while all other patients had unchanged values or a difference on the order of 0.1 mg/ml. Creatinine clearance data were available from eight patients. Apart from patient no. 2 only one other patient showed a drop in the creatinine clearance of >25% after a first cisplatin dose of 50 mg/m². In the latter patient the body weight remained exactly the same, as well as the serum creatinine level, while creatinine clearance estimation varied from +73% to −40% compared with the first determination, indicating inadequate sampling. All the other patients showed minor positive or negative changes from the original value (≤15%). In none of the patients was there any clinical evidence of development of ascites between the treatment courses.

A statistical analysis of the calculated AUCs de-

rived from the 24 treatment courses led to the following conclusions: (a) There appears to be no difference between the AUCs obtained with the lyophilized formulation and the ready-to-use solution ($p = 0.97$; 95% confidence interval: 92.5–108.8%). (b) The AUCs after the second course are significantly increased in comparison with the AUCs after the first course ($p = 0.026$). (c) The normalized AUC is independent of the administered dose ($p = 0.28$).

Although the slopes of the plasma elimination curves were significantly changed during the second cycle ($p = 0.035$), the changes were not related to the cisplatin formulation ($p = 0.82$). Computerized NLIN of the concentration–time curves in cycle 1 revealed that a triexponential curve was found to best fit the total platinum concentrations in plasma in six of the 12 courses. The other six were equally well fitted by curves with two- or three-exponential terms. In contrast, in cycle 2 only two of the 12 decay curves were best fitted with three exponential terms, while in 10 there was no preference for a bi- or triexponential curve. There was no indication that this was related to the formulation used. Cumulative urinary platinum excretion after 3 days was not related to the treatment cycle or to the formulation used.

TABLE 2. *Corrected and normalized areas under the curve (AUCs) ($t_{0-96\,h}$) related to treatment cycle and formulation*

Patient no.	Cycle no.	AUC[a] (μg Pt min/ml)		AUC/dose/m²[b]	
		Solution	Powder	Solution	Powder
1	1	11,047		110.5	
	2		12,415		124.2
2	1		10,584		105.8
	2	15,035		150.3	
3	1		6,664		88.9
	2	7,399		98.7	
4	1	6,156		82.1	
	2		7,678		102.4
5	1		7,113		142.3
	2	7,435		148.7	
6	1		9,504		126.7
	2	10,207		136.1	
7	1	6,225		124.5	
	2		6,634		132.7
8	1		9,852		100.5
	2	9,824		107.9	
9	1	7,325		122.1	
	2		7,603		126.7
10	1		7,897		123.4
	2	7,489		109.0	
11	1		11,313		113.1
	2	12,037		120.4	
12	1		7,629		101.7
	2	9,698		129.3	

Pt, total platinum in plasma.
[a] AUC *corrected*.
[b] AUC normalized.

DISCUSSION

Using a very intensive sampling scheme, the data do not indicate a difference in pharmacokinetics between the lyophilized formulation and the ready-to-use solution of cisplatin. In particular, statistical analysis of the area under the total platinum concentration–time curves did not reveal a difference in bioavailability of these species.

As shown in Table 1, differences in duration of infusion did occur in individual patients between cycles 1 and 2 (patients 3, 5, and 7). On all three occasions, infusions were more prolonged during the second cycle than during the first one. Using only the lyophilized formulation, we described earlier that a triexponential curve best fitted the total platinum concentrations up to day 5 after rapid infusions (5–15 min), while after infusions of longer duration (2–3 h) the best fit was obtained with a bi- or triexponential curve (11,12). These findings largely explain the observed changes between cycles 1 and 2 in patients 3 and 5 with respect to the NLIN curve-fitting analysis. In patients 9 and 11, a similar alteration in pattern was observed in cycles 1 and 2, as mentioned above, but without a change in infusion time. However, in only one of them was the ready-to-use formulation used during the first cycle. Therefore, the observed changes do not suggest an influence of a new formulation product.

Intraindividual variation between subsequent treatment cycles of cisplatin have not been studied systematically, to our knowledge. However, where performed, successive cisplatin courses have showed a definite cumulative effect, dependent on the administered dose and time interval between treatment cycles (12,14). In those previous studies, elimination half-lives of total platinum species were found to increase with time after the administration of cisplatin, and elimination half-life was longer after repeated cisplatin infusions as compared with those measured after the first cycle (12). No correlation was found between changes in elimination half-life and changes in renal function (based on both serum creatinine levels and creatinine clearance determinations). In contrast, urinary total platinum excretion remained the same after each

successive cycle when renal function remained normal (12). The observations in the present study, during which renal function overall remained normal, are in agreement with these previous observations. We suggested that the half-lives of total platinum species in plasma are mainly determined by the turnover rates of proteins to which these species are largely bound. If one assumes that the binding affinity to the different proteins in the plasma remains the same at subsequent cycles, the fractions with the longest half-lives will dominate at that time, which may explain the decreased slope during cycle 2 compared with cycle 1. However, this change in half-life cannot completely explain the difference in AUC between cycles 1 and 2. Therefore, a possible explanation for the increase in AUC during cycle 2 may be a difference in total body distribution of platinum species between cycles 1 and 2.

Many antineoplastic drugs have been reported to exhibit carcinogenic, mutagenic, and teratogenic properties, and this also holds for platinum complexes (15). Therefore, there is a growing awareness and concern regarding the potentially hazardous effects on those who prepare and administer these drugs (16–18). Personnel handling cytotoxic drugs may be subject to absorption of these agents through inhalation or skin absorption. There have been reports of episodes of lightheadedness, dizziness, and facial flushing in pharmacists preparing cisplatin (19). Also, detectable levels of antineoplastic drugs have been found in the air of hospital units with no ventilation hoods (20). Therefore, it is essential to reduce the risk of aerosolization to a minimum. In this respect, the ready-to-use formulation of cisplatin studied here is preferable.

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