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Pharmacokinetics of intact cisplatin in plasma. Infusion versus bolus dosing

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Summary

Plasma levels of total platinum, total filterable platinum and intact cisplatin were monitored in 4 patients who received cisplatin in a regimen consisting of 20 mg/m^2 by i.v. bolus followed immediately by 80 mg/m^2 by 6 h infusion. Baseline pharmacokinetic parameters were obtained from a previous study in which 100 mg/m^2 of cisplatin was administered by a single i.v. bolus. These baseline pharmacokinetic parameters were used in an attempt to predict the pharmacokinetic behavior of cisplatin in the present study. The results demonstrated close agreement between observed and predicted plasma level–time profiles and the area under the plasma concentration–time profiles for cisplatin. The ratios of the various platinum species in plasma over the time course of the study were also consistent with those previously reported. These findings suggest that at a dose of 100 mg/m^2, the pharmacokinetics of cisplatin and its conversion to other species in plasma are independent of dosage schedule. Since 100 mg/m^2 is a relatively high dose of cisplatin, it is likely that this approach is applicable to other doses and schedules, and ultimately might prove useful in designing optimum cisplatin dosage regimens.

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Introduction

The antineoplastic compound, cisplatin, is presently being used in the treatment of a number of tumor systems. In clinical use, the drug is administered intravenously using various treatment schedules including bolus injection (Himmelstein et al., 1981; Casper et al., 1979) and short (Patton et al., 1978; Belt et al., 1979; Gormley et al., 1979; Gullo et al., 1980) and long-term infusions (Casper et al., 1979; Patton et al., 1978; Belt et al., 1979; Gullo et al., 1980; Lokich, 1980, Jacobs et al., 1978). Most attempts at altered treatment schedules have been aimed primarily at reducing renal and gastrointestinal toxicity.

Loo et al. (1978) reported that when cisplatin is administered as a small priming dose followed by a 20 mg/m^2 infusion, daily for 5 days, that the severity of nausea and vomiting was reduced while effectiveness was maintained. Drewinko et al. (1973) also suggested that less toxicity and better antitumor activity might be possible by infusion of low doses of cisplatin. Jacobs et al. (1978) described a good response rate with minimal toxicity in treating head and neck tumors with 24-h cisplatin infusions. Although Lokich (1980) was able to reduce GI toxicity of cisplatin, over bolus schedules, by using continuous 5-day infusions, toxicity was cumulative and dose-related.

In spite of the use of varied doses and treatment schedules, very little information is available concerning the potential pharmacokinetic consequences of bolus versus infusion administration of cisplatin. Recently, Gullo et al. (1980) measured blood levels of total and filterable platinum following 1-h and 20-h infusions and reported some preliminary pharmacokinetic informaton. However, to date, only one study (Himmelstein et al., 1981) has described the clinical pharmacokinetics of intact cisplatin. That study involved only bolus administration of cisplatin.

In the present study, the pharmacokinetic behavior of intact cisplatin, total platinum and total filterable platinum was studied in 4 patients who received cisplatin by a combination of i.v. bolus and 6-h infusions. The bolus serves as a loading dose to achieve plasma levels of cisplatin which could then be maintained by the infusion. The objective was to examine similarities and/or differences in the clinical pharmacokinetics of cisplatin as a function of dosage schedule.

Materials and methods

Patients and protocol

Four patients with histologically confirmed, advanced malignancies were selected for the study. Those who received prior chemotherapy had recovered from all toxic effects with white blood cell count $> 4000/mm^3$ and platelet count $> 130{,}000/mm^3$. A minimum of 3 weeks between prior chemotherapy and entry into this study was required. The patients had normal renal function confirmed by creatinine clearance > 70 ml/min, serum creatinine ≤ 1.5 mg/ml, BUN < 20 mg%, normal urinalysis and at least one functioning, unobstructed kidney.

The patients were hospitalized and prehydrated with 2000 ml of 5% dextrose in

0.5 N saline over 12-h and were maintained on i.v. fluids for a minimum of 24 h following treatment. Each patient received 100 mg/m^2 of cisplatin in 1000 ml of sterile normal saline. The dose was divided, with 20% given by rapid injection (1–2 min) and the remainder over a nominal 6-h period by infusion pump.

Fifteen ml blood samples were withdrawn at 5 and 30 min and at 1, 2 and 4 h during infusion. An additional blood sample was taken at the end of infusion and at 1/2, 1 and 2 h following the end of infusion.

Analysis

Apparatus. Atomic absorption measurements were made with a Varian Techtron Model 175B atomic absorption spectrophotometer interfaced with a CRA-90 carbon rod atomizer. The platinum 265.95 nm line was monitored.

Materials. Ultrafiltrates were prepared with Centriflo CF-50A conical filters (Amicon, Lexington, MA). Used filters were cleaned for 30 min in distilled water in an ultrasonic bath and stored in ethanol:water (10:90 v/v).

Methods

Sample preparation. Approximately 15 ml of blood was collected in citrated tubes and centrifuged at $1000 \times g$ for 5 min. The plasma was recovered for analysis. An aliquot (about 1 ml) was transferred to a vial for subsequent total platinum determination. The remaining plasma was placed in an ultrafiltration filter cone and centrifuged for 10 min at $1000 \times g$. The resulting ultrafiltrate was transferred to a 5-ml scintillation vial, closed tightly and immediately frozen in a dry-ice–acetone bath and maintained at $< 20°C$ until analyzed (Long et al., 1980).

Total platinum assay. The plasma sample was diluted with 2 vols. of a 0.25% Triton X-100 solution and a 2-μl aliquot introduced into the carbon rod furnace of the atomic absorption spectrophotometer. The lamp current was maintained at 10 mA. A 3-stage heating program was used, consisting of drying at 90°C for 50 s, ashing at 1200°C for 15 s and atomizing at 2300°C. The ramp rate of the program was 400°C/s. Nitrogen flow rate was maintained at 4 l/min.

Filterable platinum assay. The ultrafiltrate was thawed and a 2-μl aliquot introduced directly into the carbon rod furnace. Conditions for the atomic absorption analysis were identical to those used for total platinum measurement. In this study, filterable platinum levels are the total amount of platinum present in the ultrafiltrates.

Cisplatin. An aliquot (50 μl) of the ultrafiltrate was subjected to HPLC analysis on a strong anion-exchange resin with methanol:acetate buffer (0.1 M; pH 3.8) (1:1) as mobile phase according to the procedure of Chang et al. (Chang et al., 1978). Using a flow rate of 2 ml/min, the fraction eluting 3–5 min post-injection

was collected. The mobile phase was evaporated to dryness and the residue reconstituted with 50 μl of 0.01 M NaCN solution. A 2-μl aliquot of the final solution was analyzed for platinum by atomic absorption spectroscopy as described above with the following minor modifications in the heating program: drying at 90°C for 40 s, ashing at 1200°C for 5 s and atomizing at 2300°C. Ramp rate was 400°C/s.

Results and Discussion

Tables 1–4 show the plasma levels of total platinum, total filterable platinum and cisplatin obtained in each of the 4 patients as well as the ratios between the species measured. It should be noted that although the dose (100 mg/m^2) and schedule (20% bolus, 80% infusion) was the same in all cases, the infusion rate varied somewhat due to imprecision in the pump setting.

It can be seen from the tables that total platinum levels decline only very slowly following termination of infusion. This is indicative of the fact that distribution is essentially completed during the period of infusion and also reflects the very long terminal half-life of total platinum in plasma. However, both total filterable and cisplatin plasma levels decline rapidly following termination of infusion. This, too, is consistent with the short plasma half-lives of these species as reported previously (Himmelstein et al., 1981; Patton et al., 1978; Belt et al., 1979). Due to the fact that only 2–3 plasma samples were obtained after infusion (due to sensitivity limitations of the analytical methods), no attempt was made in this study to quantitate the half-lives of these species.

TABLE 1

PLASMA LEVELS AND SPECIES RATIOS OF TOTAL PLATINUM, TOTAL FILTERABLE PLATINUM AND CISPLATIN FOLLOWING DOSING OF 100 mg/m^2 OF CISPLATIN BY BOLUS (20%) AND INFUSION (80%)—PATIENT no. 1 [a,b]

Time (min)	Concentration in plasma (μg/ml)			Cisplatin : total platinum ratio	Cisplatin : total filterable platinum ratio
	Total platinum	Total filterable platinum	Cisplatin		
5	1.17	0.68	0.47	0.40	0.69
30	0.62	0.59	0.36	0.58	0.61
60	0.67	0.32	0.36	0.54	1.12
120	0.81	0.35	0.37	0.46	1.06
245	1.49	0.35	0.30	0.20	0.86
384	2.06	0.43	0.38	0.18	0.88
414	1.92	0.21	0.23	0.12	1.10
444	1.70	0.16	0.13	0.08	0.81
504	1.78	bld [c]	bld [c]		

[a] Total dose was 160 mg (32 mg bolus, 128 mg infusion).
[b] Infusion time was 6 h and 24 min (384 min).
[c] Below limits of detection.

TABLE 2

PLASMA LEVELS AND SPECIES RATIOS OF TOTAL PLATINUM, TOTAL FILTERABLE PLATINUM AND CISPLATIN FOLLOWING DOSING OF 100 mg/m^2 OF CISPLATIN BY BOLUS (20%) AND INFUSION (80%)— PATIENT no. 2 [a,b]

Time (min)	Concentration in plasma (μg/ml)			Cisplatin : total platinum ratio	Cisplatin : total filterable platinum ratio
	Total platinum	Total filterable platinum	Cisplatin		
7	0.94	0.79	0.33	0.35	0.42
30	0.88	0.86	0.63	0.72	0.73
60	1.06	0.71	0.54	0.51	0.76
120	1.16	0.56	0.39	0.33	0.70
240	1.71	–	0.36	0.21	–
335	1.81	0.70	0.38	0.21	0.54
365	1.77	0.41	0.23	0.13	0.56
385	1.66	0.19	0.10	0.06	0.53
455	1.99	0.04	bld [c]		

[a] Total dose was 170 mg (34 mg bolus, 136 mg infusion).
[b] Infusion time was 5 h and 35 min (335 min).
[c] Below limits of detection.

TABLE 3

PLASMA LEVELS AND SPECIES RATIOS OF TOTAL PLATINUM, TOTAL FILTERABLE PLATINUM AND CISPLATIN FOLLOWING DOSING OF 100 mg/m^2 OF CISPLATIN BY BOLUS (20%) AND INFUSION (80%)—PATIENT no. 3 [a,b]

Time (min)	Concentration in plasma (μg/ml)			Cisplatin : total platinum ratio	Cisplatin : total filterable platinum ratio
	Total platinum	Total filterable platinum	Cisplatin		
5	1.38	1.16	0.83	0.60	0.72
30	0.73	0.66	0.41	0.56	0.62
60	0.89	0.54	–	–	–
120	1.16	0.67	0.39	0.34	0.58
240	1.20	0.48	0.33	0.28	0.69
370	2.11	0.58	0.35	0.16	0.60
400	1.82	0.42	0.23	0.13	0.55
430	1.69	0.23	0.12	0.07	0.52
490	1.67	0.14	bld [c]		

[a] Total dose was 160 mg (32 mg bolus, 128 mg infusion).
[b] Infusion time was 6 h and 10 min (370 min)
[c] Below limits of detection.

TABLE 4

PLASMA LEVELS AND SPECIES RATIOS OF TOTAL PLATINUM, TOTAL FILTERABLE PLATINUM AND CISPLATIN FOLLOWING DOSING OF 100 mg/m^2 OF CISPLATIN BY BOLUS (20%) AND INFUSION (80%)—PATIENT no. 4 [a,b]

Time (min)	Concentration in plasma (μg/ml)			Cisplatin: total platinum ratio	Cisplatin: total filterable platinum ratio
	Total platinum	Total filterable platinum	Cisplatin		
5	1.26	1.02	1.00	0.79	0.98
30	1.06	0.61	0.43	0.41	0.70
60	0.94	0.56	0.47	0.50	0.84
120	0.86	0.32	0.28	0.32	0.88
240	1.39	0.38	0.28	0.20	0.74
360	0.60	0.38	0.27	0.45	0.71
420	1.95	0.41	0.27	0.14	0.66
480	2.02	0.19	0.14	0.07	0.74
540	1.84	bld [c]	bld [c]		

[a] Total dose was 190 mg (40 mg bolus, 150 mg infusion).
[b] Infusion time was 7 h (420 min).
[c] Below limits of detection.

In a previous communication (Himmelstein et al., 1981), we reported that the ratio of cisplatin to total platinum plasma levels decreased continuously after bolus injection, from about 0.5 at 5 min to about 0.1 at 2 h. The ratio of cisplatin to total filterable platinum in plasma, however, remained constant at about 0.6–0.8 over the time period during which they could be detected. The trend towards a continual decline in cisplatin:total platinum ratio and constant cisplatin:total filterable platinum ratio in plasma was similarly observed in the present study, as shown in Tables 1–4.

The observations that: (a) the gross shape of the plasma concentration decline for the 3 species; and (b) the species ratios do not change as a function of method of administration, led to a more detailed analysis of the effect of dose schedule on cisplatin plasma levels. It was speculated that if cisplatin levels are independent of the method of administration that it may be possible to use a simple pharmacokinetic method to predict cisplatin levels regardless of the dosing schedule. Such predictability could be important ultimately in designing dosage regimens of cisplatin based on therapeutic and toxic drug levels.

To examine the possibility of predicting cisplatin plasma levels, the data from the previous study (Himmelstein et al., 1981) were used to obtain baseline pharmacokinetic parameters. From that study the data from 6 patients were chosen who had received 100 mg/m^2 of cisplatin without mannitol by i.v. bolus injection. Using the mean plasma levels of these 6 patients, the following pharmacokinetic parameters for cisplatin were calculated (mean dose = 180 mg); area under the plasma concentration time curve (0–120 min) = 104 μg · min · ml^{-1}, elimination rate constant = 2.48

$\times 10^{-2}$ min^{-1}, $t_{1/2} = 27.9$ min, extrapolated plasma concentration at time zero = 31.3 μg/ml and volume of distribution = 57.5 liters.

Using these parameters, a hypothetical case was considered in which cisplatin was dosed (180 mg or 100 mg/m^2), 20% by bolus and 80% by 6 h infusion. For a drug which declines from the plasma monoexponentially such as cisplatin (Himmelstein et al., 1981), plasma levels following combination bolus and infusion dosing can be described by Eqn. 1 (Gibaldi and Perrier, 1975):

$$C = C_0 e^{-Kt} + \frac{k_o}{VK}(1 - e^{-Kt}) \quad (1)$$

where C is the plasma concentration at any time, C_0 the initial concentration following a single dose, K the elimination rate constant, t is time, k_0 the infusion rate and V the volume of distribution. At steady-state, this expression simplifies to Eqn. 2

$$C_{ss} = \frac{k_0}{VK} \quad (2)$$

which describes the plateau plasma levels, C_{ss}, for a drug given by i.v. infusion.

The hypothetical values obtained using the above treatment were compared to those obtained in the individual patients in this study. Cisplatin plasma levels in a representative patient are shown in Fig. 1 compared to the hypothetical case. Also shown in this figure are the plasma levels obtained in the previous study (Himmelstein et al., 1981) from which the original pharmacokinetic parameters were generated.

Several important points are evident from our examination of the data. First, the hypothetical profile has a calculated AUC of 113 $\mu g \cdot min \cdot ml^{-1}$ (5 min to end of infusion). The AUCs for the 4 patients studied here were 137, 132, 139 and 137. The agreement with prediction is reasonable considering both patient variability and the variations in the infusion rates. Secondly, the hypothetical case predicts plateau cisplatin levels of 0.28 μg/ml. Tables 1–4 show that the actual plateau values for cisplatin in the 4 patients had a mean of approximately 0.35 μg/ml. Finally, the consistency of hypothetical and actual patient plasma levels indicates that with a given dose, the pharmacokinetic behavior of cisplatin is independent of the method of administration.

The consistency of pharmacokinetic parameters for other platinum species (total platinum and filterable platinum), regardless of dosing schedule has been pointed out recently by Gullo et al. (1980) using 1-h and 20-h infusions. In that study the volume of distribution of total platinum was shown not to be dependent on the length of infusion. However, they (Gullo et al., 1980) were not able to monitor filterable plasma levels in the 20-h infusion and they did not monitor intact cisplatin. It appears that the present study is, therefore, the first to describe the pharmacokinetic behavior of intact cisplatin as a function of dosing schedule.

In summary, pharmacokinetic parameters for cisplatin following bolus dosing

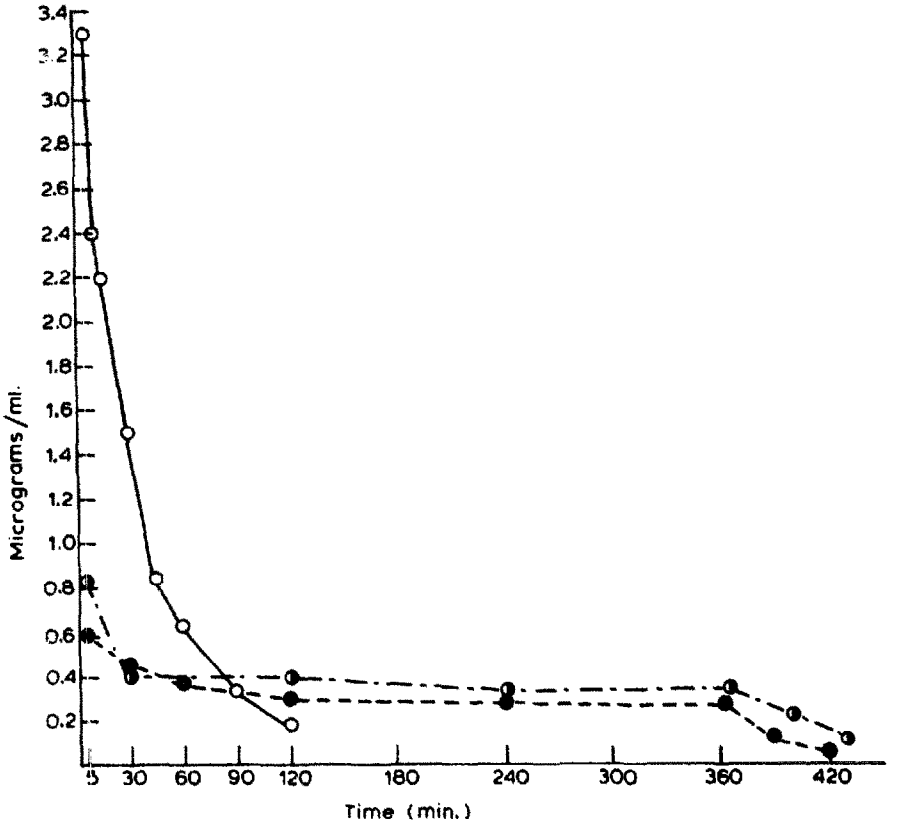

Fig. 1. Plasma levels of cisplatin in humans following intravenous doses of 100 mg/m^2. Open circles represent mean plasma levels in 6 patients after bolus dose; filled circles represent the hypothetical profile when 20 mg/m^2 are given by bolus and 80 mg/m^2 by 6-h infusion using the pharmacokinetic parameters obtained from the open-circle profile; half-filled circles represent the plasma level profile obtained in a representative patient (no. 3) when 20 mg/m^2 were given by bolus and 80 mg/m^2 were given by a 6-h and 10-min infusion.TABLE I

were used to predict cisplatin plasma levels when the same dose was given 20% by bolus and the remainder by i.v. infusion. The consistency of the shape of the profiles observed with that predicted, the agreement of hypothetical with observed AUCs and plateau levels, and the consistency of the species ratio with those observed previously offers strong evidence that the pharmacokinetics of cisplatin and its conversion to other species in plasma are independent of dosage schedule.

As was pointed out by Gullo et al. (1980), these results do not suggest that one of these schedules is necessarily clinically superior to the other. Furthermore, these results should probably be confirmed in a larger patient population. What is suggested, however, is that it does not appear that different schedules appreciably change the pharmacokinetics of cisplatin itself. If such is the case, it should be possible to design safe and effective dosage regimens of cisplatin, should therapeutic and toxic levels of this drug be defined.

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