Pharmacokinetics of Free Platinum Species following Rapid, 3-hr and 24-hr Infusions of cis-Diamminedichloroplatinum (II) and its Therapeutic Implications

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Abstract—The pharmacokinetics of free platinum species derived from cis-diamminedichloroplatinum (II) (cisplatin) was studied in three patients who received the drug as a single agent for the first time at equal doses (100 mg/m²) but with different infusion times. In rapid, 3-hr and 24-hr infusions, peak levels of free platinum were 8.62, 1.96 and 0.27 µg Pt/ml respectively; half-lives of disposition calculated 0–30 min after the end of each infusion were 17.4, 22.7 and 26.2 min respectively. Free platinum availability, measured as the area under the curves of the free platinum concentration, was the same for the three modes of administration (290, 321 and 325 µg Pt/min/ml⁻¹ respectively). This observation supports the clinical impression that antitumour activity of cisplatin is not dependent on the method of administration.

INTRODUCTION

cis-DIAMMINEDICHLOROPLATINUM (II) (cisplatin) is one of the most effective antineoplastic agents for certain tumour types, such as testicular cancer, ovarian cancer, bladder cancer and head and neck cancer [1, 2]. The drug may cause distressing gastrointestinal toxicity, in particular nausea and vomiting, sometimes leading to treatment refusal. Other side effects include renal toxicity, which is cumulative and dose-limiting, ototoxicity, myelosuppression and neurotoxicity [3]. Various methods have been investigated in order to reduce these toxic effects, including continuous infusion techniques [4–8]. From in vitro experiments, Drewinko et al. suggested an increased antitumour effect of cisplatin with an improved therapeutic index by low-dose infusions [9]. In preclinical animal studies the drug was not found to be schedule-dependent for activity in the L1210 leukemia [10]. In some clinical studies using prolonged infusions of cisplatin, less gastrointestinal toxicity and/or renal toxicity was

observed [4, 5, 7, 8]. There are no studies indicating an improved antitumour effect for a particular method of administration. While non-protein-bound platinum probably represents biologically active platinum species in plasma [11, 12], experiments in the rat made it very unlikely that the protein-bound fraction contributed to the toxicity observed during cisplatin treatment [13]. Therefore free platinum measurements in plasma are of interest in patients receiving the drug by different modes of administration, both with regard to antitumour effect and also to drug-induced toxicity. In the present study cisplatin was administered to 3 patients at the same dose, either as a rapid infusion, a 3-hr infusion or a 24-hr infusion. Plasma concentrations of total and free platinum were assayed and urinary excretion was measured. A comparison was made for the total exposure to the free drug during and after administration of cisplatin in the three patients.

MATERIALS AND METHODS

Patients

All 3 patients in the study received cisplatin for the first time as a single agent in a dose of 100 mg/m². The first patient (A) was a 63-yr-old

man with a recurrent carcinoma of the tongue, who received cisplatin by a rapid infusion (8 min). The second patient (B) was a 70-yr-old woman with a stage IV ovarian carcinoma resistant to conventional chemotherapy. She received the drug over a 3-hr period. The third patient (C) was an 80-yr-old man with a squamous cell carcinoma of the base of the tongue, recurrent after prior radiotherapy and chemotherapy. This patient received cisplatin by a continuous infusion for 24 hr. All 3 patients had normal renal function (serum creatinine 70–80 μmol/l) and normal liver function (bilirubin, alkaline phosphatase, transaminases). Patient B had ascites at the time therapy was started.

Study design

All 3 patients received cisplatin prepared from vials of Platinol®. Each vial contained 10 mg of cisplatin, 90 mg of sodium chloride and 100 mg of mannitol. After reconstitution with sterile water, a concentration of 1 mg cisplatin/ml was obtained. The drug was used immediately after preparation, without further dilution, and administered via a pump system. All patients received 1 l. of normal saline during the 4-hr period preceding cisplatin administration. Further hydration was performed during and up to 24 hr after administration of cisplatin at a rate of 1 l. per 6 hr. Mannitol and furosemide were not used on a routine base. In case diuresis was less than 600 ml over a 6-hr period, 100 ml mannitol 20% was given i.v. at that time. If indicated, this was repeated after 2 hr in combination with 5 mg furosemide. None of the patients received mannitol before or during the administration of cisplatin, or within 6 hr thereafter. On the day of cisplatin administration and then for as long as necessary, metoclopramide was given at a dose of 20 mg t.i.d. orally for control of emesis.

Blood samples were drawn in heparinized tubes prior to administration of cisplatin, at the end of infusion, and 10, 20, 30, 60, 90, 120, 150, 180, 210 and 240 min and 6, 8, 21 and 24 hr following the infusion. In addition, samples were drawn during infusion at 0.5, 1 and 2 hr after the start of infusion in patient B and 3, 6, 12 and 20 hr after the start in patient C. After the first 24-hr observation period blood samples were taken daily (24-hr intervals) for at least 5 days. For analysis of the free platinum concentrations, the same time points during infusion were used as for the total platinum measurements and also up to 4.5 hr after the end of infusion. All samples were centrifuged on the spot and plasma was removed. Four millilitres of plasma were ultrafiltrated by means of Amicon Centriflo CF50A cones. The ultrafiltrate fraction of 600–1100 μl was used for determination of the free platinum concentrations. All plasma and

ultrafiltrate samples were stored at –30°C until analysis. Urine collection was started just before administration of cisplatin. No patient was catheterized. Due to excessive diarrhoea, urine collection in patient B was considered to be unreliable. During infusion, 6-hr samples were collected in patient C. Furthermore, 6-hr samples were collected during the first 24-hr period after the end of infusion in patients A and C. After the first day, 24-hr samples were collected for at least 5 days. Aliquots were stored at –30°C until analysis.

Platinum analysis

Plasma, ultrafiltrate and urine samples were thawed just before analysis and diluted (1:1 v/v for plasma and 9:1 v/v for ultrafiltrate and urine) with a solution of 0.15 M NaCl in 0.4 N HCl for plasma and 0.6 M NaCl in 2 N HCl for urine and ultrafiltrate. The concentrations of platinum in the samples were then determined by flameless atomic absorption spectrometry using a Perkin Elmer atomic absorption spectrophotometer No. 373. The conditions were: for plasma, 40 sec drying at 125°C, 120 sec thermal decomposition at 1400°C and 10 sec atomization at 2650°C; for ultrafiltrate and urine, 30 sec drying, 25 sec thermal decomposition and 10 sec atomization at the same temperatures as for plasma. Ramps were used between the steps. The precision of the assay (C.V.) was 1.8% at a concentration of 0.5 μg Pt/ml, 4.5% at a concentration of 1 μg Pt/ml, 2.7% at a concentration of 2 μg Pt/ml and 2.5% at a concentration of 3 μg Pt/ml ($n = 12$ at each concentration level).

RESULTS

Semilogarithmic plots of the total platinum concentrations in plasma and free platinum concentrations in the ultrafiltrate vs time are shown in Figs. 1, 2 and 3 for patients A, B and C respectively. Peak levels of total platinum differed in the three types of infusion. However, concentrations measured 24 hr after the end of infusion were comparable, being 1.44 μg/ml, 1.48 μg/ml and 1.47 μg/ml in patients A, B and C respectively.

After the rapid infusion of cisplatin, a biexponential decline of total platinum levels was observed. The fast initial decline was much less pronounced after the 3-hr and 24-hr infusions. Half-lives of elimination of total platinum (calculated from days 1–5) were 7.2, 8.0 and 7.5 days in patients A, B and C respectively. After rapid infusion, peak levels of filterable platinum corresponded to the peak level of total platinum (both 8.62 μg/ml). In patient B those values were different (1.96 μg/ml and 2.72 μg/ml respectively). In patient C the total platinum peak level was
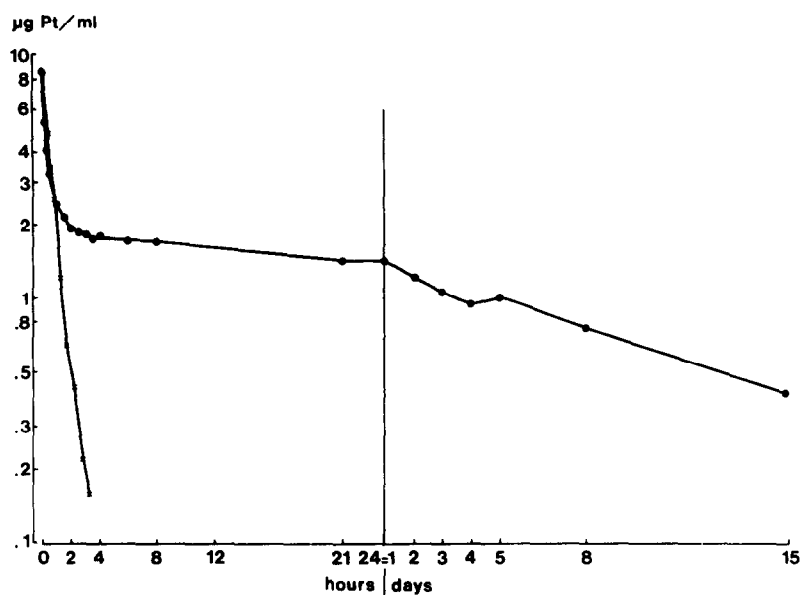
Fig. 1. *Semilogarithmic plot of total platinum concentrations in plasma* (●———●) *and free platinum concentrations in plasma ultrafiltrate* (×———×) *vs time in patient A, receiving* 100 mg/m² *cisplatin* (=146.3 mg Pt) *in* 8 min.
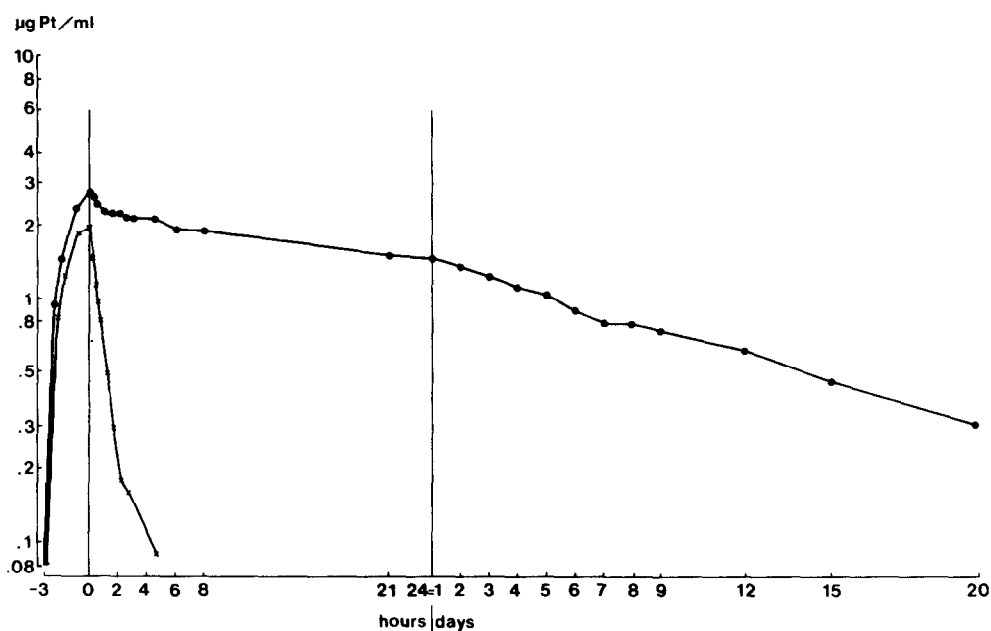

Fig. 2. *Semilogarithmic plot of total platinum concentrations in plasma* (●———●) *and free platinum concentrations in plasma ultrafiltrate* (×———×) *vs time in patient B, receiving* 100 mg/m² *cisplatin* (=100.8 mg Pt) *in* 3 hr. *The concentrations during infusion* (-3 *to* 0 hr) *and up to* 24 hr *after infusion are plotted against time in hours, thereafter in days.*

about 9 times higher than the free platinum peak level (2.35 μg/ml vs 0.27 μg/ml). During the 24-hr infusion a steady state of free platinum levels was reached after 3 hr from the start of the infusion, while total platinum levels gradually built up until the end of the infusion. After 3 hr 39.5% of the plasma platinum was bound, while after 24 hr this was 89%. The slightly rising free and total platinum concentrations between 21 and 24 hr of infusion could have resulted from an increased

inflow by the pump near the end of the infusion. The decrease in free platinum levels after the end of the infusions appeared not to be a first order decay. On a semi logarithmic scale a good linear fit could only be obtained from 0 to 30 min. Half-lives of free platinum after the 3 types of infusions are shown in Table 1, all calculated during the time interval 0-30 min.

In order to be informed about the total amount of free platinum available to the tissues during and
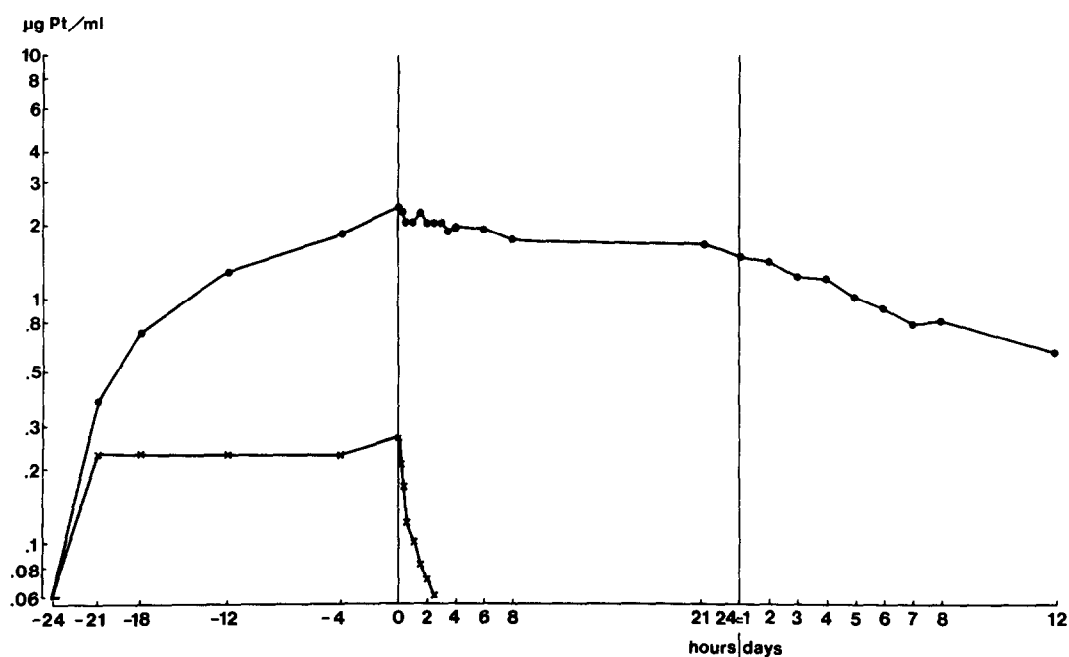
μg Pt/ml

Fig. 3. Semilogarithmic plot of total platinum concentrations in plasma (●———●) and free platinum concentrations in plasma ultrafiltrate (×———×) vs time in patient C, receiving 100 mg/m² cisplatin (=128.7 mg Pt) in 24 hr. The concentrations during infusion (-24 to 0 hr) and up to 24 hr after infusion are plotted against time in hours, thereafter in days.

Table 1. Pharmacokinetic parameters of free platinum in plasma ultrafiltrate from patients receiving 100 mg/m² cisplatin by rapid, 3-hr and 24-hr infusion

Patient	Infusion time	Total dose elemental Pt (mg)	$t_\frac{1}{2}$ (min)	AUC (μg Pt. min/ml)
A	8 min	146.3	17.4	290
B	3 hr	100.8	22.7	321
C	24 hr	128.7	26.2	325

after the infusions, areas under the curves (AUCs) were determined for all 3 free platinum concentration vs time curves. As shown in Table 1, the AUCs were similar for the 3 types of infusion. Urinary excretion of platinum was rapid during infusion and during the first hours thereafter. In patient A 21.4% of the administered dose was excreted during the first hour, while only 6.7% was recovered during the following 5 hr. Twenty-four hours and 8 days after the infusion 32.0 and 47.6% of the administered dose had been excreted respectively.

In contrast to these findings, the excretion during the 24-hr infusion of cisplatin in patient C was lower during the first 24 hr (17.6%). After 8 days 33.1% of the administered dose had been excreted. Apart from the initial 24-hr period the slopes of the cumulative urinary excretion curves were similar regardless of cisplatin infusion rate in those 2 patients.

In patient C free platinum clearance was 68 ml/min during the period of steady state of free

platinum levels during infusion. The pre-treatment creatinine clearance in this patient had been 78 ml/min. This indicated that renal excretion of free platinum species had been primarily caused by glomerular filtration.

DISCUSSION

The patterns of the total platinum concentrations in plasma after administration of 100 mg/m² cisplatin observed in the present study are in agreement with data from the literature [12, 14–19]. Half-lives of elimination appear to be longer than those found in former studies, where there had been a limited observation period of only 24 or 48 hr after termination of the infusion. However, the findings do correspond closely to those reported in studies in which sample analysis had been performed for a longer period of time [15–17]. This difference can be explained by the elevation of plasma platinum levels during the first 24 hr due to secondary influx of platinum in

the plasma compartment e.g. by enterohepatic circulation [17].

Free platinum concentrations were detectable up to 3.5 hr after the end of the rapid infusion, during 2.5 hr after the 3-hr infusion and up to 1 hr after the end of the 24-hr infusion. These differences can be explained by distribution and protein binding during infusion. Free platinum levels did not decrease by first order decay. This is probably a result of the elimination process, transport to peripheral compartments and protein binding, as well as the second influx after enterohepatic circulation. These processes also occur during infusion and explain the increase in half-lives of free platinum concentrations after infusions with increasing administration times. Overall, half-lives of free platinum found in our study are in agreement with those found by others, ranging from 11.7 to 30 min [16, 18, 20, 21].

In contrast to the report of Jacobs *et al.* [19], in which free platinum clearance exceeded creatinine clearance during 24-hr infusion of cisplatin, we did not observe this in our patient. It thus remains unclear whether free platinum is primarily cleared by glomerular filtration, as suggested earlier [12], or whether there is additional tubular excretion.

The AUCs of the free platinum levels are a measure of the overall availability of these species. Since only free circulating platinum species appear to have cytotoxicity, the equivalence of the AUCs after the rapid, 3-hr and 24-hr infusions could correlate with a therapeutic equivalence of the three types of infusion.

In two studies intact cisplatin has been determined [22, 23]. In the first study patients received cisplatin by an i.v. bolus injection, and pharmacokinetic parameters for cisplatin obtained from this study were used to predict cisplatin plasma levels when the same dose was given 20% by bolus and the remainder by a 6-hr i.v. infusion, as was done in the second study. In this latter study concentrations of intact cisplatin in plasma were measured in 4 patients. The predicted and observed concentration vs time curves were in close agreement and the authors concluded that at the dose of 100 mg/m² the

pharmacokinetics of cisplatin and its conversion to other species seemed to be independent of dose schedule [23]. Our study compares for the first time the free platinum kinetics after rapid infusion with commonly used 24-hr and 3-hr infusions.

Apart from interesting aspects on antitumour activity in infusions of different duration, recent studies with altered infusion schemes have focused on reduction of toxicity.

At the moment little is known about the minimal concentration of free platinum that is therapeutic. *In vitro* studies suggest a higher therapeutic index with prolonged low-dose infusions than with short-term infusions [9]. An improved tolerance has been described with 5-day continuous i.v. infusion relative to bolus i.v. injection of a total dose of 100 mg/m² of cisplatin [5]. Lokich found a higher therapeutic index with this method of administration as result of a decrease in acute gastrointestinal toxicity [8]. Less renal toxicity has been reported in some non-randomized studies using prolonged infusions [4, 5, 7]. In those studies antitumour activity was comparable to that reported after rapid infusions in earlier publications. In a partially randomized trial, bolus administration was compared to 24-hr or 48-hr infusions. Renal and gastrointestinal toxicity were not improved by these prolonged infusions, while antitumour activity was equal [6]. Recently, it has been suggested that audiometric abnormalities are correlated with the method of administration, the highest incidence being associated with bolus injection [24].

Our observation in a limited number of patients suggests that if there is an improved therapeutic index with prolonged infusions, this might be explained by the fact that despite low peak concentrations of free platinum during this type of infusion, the AUCs were similar to infusions of short duration when equal doses had been used. If such is the case, then peak levels do not seem to play a major role in the antitumour activity, while they might influence the extent of toxicity. Further studies in a larger number of patients will be needed to substantiate this hypothesis.

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