Pharmacokinetics of Free and Total Platinum Species After Short-Term Infusion of Cisplatin

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

Pharmacokinetic studies were performed in ten patients who received short-term (4–15-min) infusions of cisplatin. Computerized nonlinear least-squares analysis (NLIN) and an adapted curve-stripping approach (CSTRIP) were used to characterize total-platinum concentration-time curves. The overall curves showed a rapid initial phase and a prolonged terminal phase, separated by a phase with secondary peaks attributed to the existence of an enterohepatic recirculation. Up to Day 5, NLIN analysis revealed three exponential phases, with half-lives of 14.4 mins, 273.7 mins, and 5.3 days, respectively. However, a significant consistent divergence ($P < 0.005$) was found between the observed and predicted curves during the intermediate phase, not justifying the use of an exponential function during this phase. The shape of the intermediate curve was strongly suggestive of a second influx in the plasma compartment, the amount of which was estimated by the CSTRIP approach (1.4% ± 0.5% of the administered dose). Free-platinum levels declined in a biphasic manner (half-lives: $9.7 \pm 0.2$ and $40.4 \pm 2.5$ mins; $n = 3$). After administration of 100 mg/m² of cisplatin, maximum platinum levels in rbcs ranged from 0.51 to 0.58 $\mu$g/ml and were reached within 90–150 mins. Thereafter, rbcs platinum levels declined in a biphasic fashion, with a terminal half-life, for the interval Days 5–15, of 36–47 days. The binding of platinum to both plasma proteins and rbcs in vitro (using patients' own blood) was slow, biphasic, and irreversible. [Cancer Treat Rep 68:505–513, 1984]

The antineoplastic agent cisplatin is active against a variety of tumor types (1–6). Many pharmacokinetic studies have analyzed the kinetics of cisplatin in man (7–29), but in most of them the observation period was limited to 2 days and free (unbound) platinum concentrations were not determined. Plasma clearance of total platinum after single doses of cisplatin has generally been reported to be biphasic, but in a limited number of reports three or four exponential terms have been described (11,13,28,29). The major pathway of excretion of platinum species is via the urine. However, limited amounts are excreted via the bile (23). In an earlier report we suggested the existence of an enterohepatic recirculation (EHC) in one patient (24).

In the present study cisplatin was administered by short-term infusion (4–15 mins) and was given in either low doses (40–50 mg/m²) or a high dose (100 mg/m²). The purpose of the study was to evaluate the pharmacokinetics of free and total platinum, and additionally to obtain pharmacokinetic evidence of an EHC. The patients' own blood was used separately for in vitro studies performed to investigate the binding of cisplatin to plasma proteins and rbcs.

MATERIALS AND METHODS

Patients

Ten patients (seven males, three females) were entered in the study. All patients received cisplatin as a single agent, and all but one had never received cisplatin before. The diagnoses were head and neck cancer (eight patients), urethral cancer (one patient), and ovarian cancer (one patient).

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2Department of Oncology (J. B. Vermorken, H. E. Gall, and H. M. Pinedo) and Research Laboratory of the Department of Internal Medicine (W. J. F. van der Vijgh and I. Klein), Free University Hospital, Amsterdam, The Netherlands.
3Netherlands Cancer Institute, Amsterdam.
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5Reprint requests to: J. B. Vermorken, MD, Department of Oncology, Free University Hospital, PO Box 7007, 1007 MB Amsterdam, The Netherlands.
Seven patients (Nos. 1-7, table 1) had a normal renal function (serum creatinine < 1.35 mg/100 ml, creatinine clearance \( \geq 65 \) ml/min/1.73 m²), a normal hepatic function, and no signs of ascites or pleural effusion. The mean age of this group of patients was 58 yrs (range, 42–74).

The remaining three patients formed a separate group. Patient 8 (59 yrs of age) had an increase in serum creatinine prior to treatment (1.58 mg/100 ml) and had an ureterointestinal anastomosis. Patient 9 (69 yrs of age) received a prolonged posthydration scheme (2 L/24 hrs; Days 2–5). Patient 10 (48 yrs of age) had received two courses of cisplatin before and had been treated for a septic shock during the second treatment course. Serum creatinine was still within the normal range, but creatinine clearance (65 ml/min/1.73 m²) was 50% of its original value.

**Study Design**

All patients received cisplatin prepared from vials of Platinol. After reconstitution with sterile water the solution containing 1 mg/ml of cisplatin was used immediately after preparation. Dosage and duration of infusion are specified for each patient in table 1.

All patients but one received 1 L of normal saline during the 4-hr period preceding cisplatin administration, and 4 L of saline over the 24-hr period following drug administration (Patient 3 received 5% dextrose). Mannitol and furosemide were not used on a routine basis and none of the patients received one or both diuretics before, during, or within 6 hrs after cisplatin administration.

Blood of two patients (Nos. 2 and 3) was sampled (80 ml) prior to administration of cisplatin for in vitro binding experiments. Blood samples of all patients were drawn into heparinized tubes prior to administration of cisplatin, at the end of infusion, and 5, 10, 15, 30, 60, 90, 120, 150, 180, 210, and 240 mins and 6, 8, 21, and 24 hrs after infusion. Thereafter, blood samples were taken daily (24-hr intervals) for at least 1 week. Urine collection was started just before administration of cisplatin; 6-hr samples were collected during the first 24-hr period, while thereafter, 24-hr samples were collected for at least 1 week.

All blood samples were centrifuged immediately and the plasma was removed. For three patients (Nos. 1–3) 4-ml plasma samples were filtered through Amicon Centriflo CF50A cones and the ultrafiltrate fraction of 600–1100 \( \mu l \) was used for the determination of the free-platinum concentration. Rbc's of the same patients were washed twice with an equal volume of normal saline and centrifuged at 1000 \( \times g \) for 10 mins. Rbc's, plasma, ultrafiltrate, and aliquots of 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 ultrafiltrate and urine) with a solution containing 0.4 N HCl and 0.15 M NaCl for plasma and 0.6 M NaCl in 2 N HCl for urine and ultrafiltrate. Thawed rbc's were disrupted in an ultrasonic bath for 10 mins. An 0.5-ml aliquot of lysate was digested by 3 ml of 65% HNO₃ at 170°C in a polytetrafluoroethylene (PTFE) bomb for 2 hrs. The remaining liquid was evaporated at 120°C under a stream of air after addition of 5 mg of NaCl. The residue was dissolved in 1 ml of 0.2 N HCl-0.15 M NaCl.

The concentration of platinum in all samples was deter-
mined by flameless atomic absorption spectrometry. The precision of the assay (C.V.) was about 3% in the concentration range of 0.5-3.0 µg of Pt/ml.

**In Vitro Studies**

The binding of cisplatin to plasma proteins and the rbcs was studied separately in vitro. One milliliter of a cisplatin solution containing 2.1 mM cisplatin (≈ 400 µg of Pt/ml), 0.4 N HCl, and 0.15 M NaCl was added to 40 ml of plasma of each of the two patients. The incubation was performed under mild shaking in the dark at 37°C for 24 hrs. Four-milliliter aliquots were drawn at 0, ½, 1, 2, 4, 8, and 24 hrs. All aliquots were ultrafiltered immediately after withdrawal. The total-platinum concentration was determined at the start and after 24 hrs of incubation.

Release of platinum from plasma proteins was studied with a Dianorm apparatus with 24 cells. Each cell consisted of two PTFE half-cells of 1 ml each, separated by a spectrapor membrane (cut-off, 12,000–14,000 daltons). One half-cell was filled with 1 ml of plasma and the other with 1 ml of plasma preincubated with cisplatin solution for 24 hrs at 37°C. The cells were incubated at 37°C under rotation. The platinum content was analyzed in both half-cells of two cells withdrawn daily for 8 days.

Binding of cisplatin to rbcs was studied by mixing 7 ml of rbcs with 7 ml of 0.05 mM cisplatin (≈ 10 µg Pt/ml) in 0.15 M NaCl. The incubation was performed under mild shaking in the dark at 37°C for 24 hrs. One-milliliter aliquots were withdrawn at 0, ½, 1, 2, 4, 8, and 24 hrs. All aliquots were centrifuged immediately after withdrawal. The supernatants were separated for determination of the platinum concentration.

**Method of Data Analysis**

Curves of total-platinum concentration versus time in plasma were studied in two different ways. Computerized curve-fitting was performed with the NLIN method of Marquardt (30) as implemented by Hewlett-Packard for the HP 9845A. The second method used was CSTRIP, which was applied so that the linear least-squares fit of the concentrations on Days 1–5 was subtracted from the first part of the curve, followed by a linear least-squares fit of residual concentrations during the first 0–15 mins (C₃₋₅). Next, the residuals of the remaining intermediate phase (15 mins–24 hrs) were also diminished by the extrapolated values of the first phase. The final residuals (C₅₋₂₄₋₂₅₋₃₋₅) obtained by this procedure were analyzed separately.

**RESULTS**

**Clinical Pharmacokinetics**

A semilogarithmic plot of the total-platinum concentrations in plasma versus time is shown for all patients in figure 1. All curves (except that of Patient 8, with limited sampling) showed positive deviations between 2 and 8 hrs after administration, and in six patients a small peak was observed 3–4 hrs after the end of the infusion. This phenomenon indicates a physiologic cause and could be explained by a second influx of platinum into the plasma compartment. With the NLIN analysis, a triexponential curve was found to best fit total-platinum levels for all patients over the first 5 days. The corresponding calcu-

<table>
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<th>SD of observation (%)</th>
<th>Intercepts (µg/ml)*</th>
<th>CSTRIP</th>
</tr>
</thead>
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<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>3.5</td>
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<td>5.3</td>
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lated pharmacokinetic parameters are summarized in table 1. The use of an exponential function during the second phase became questionable because of consistent deviations from the model during this phase (β-half-life × 5 = 1370 mins), and was beyond the influence of the α-phase (α-half-life × 5 = 70 mins). As a rule, the ratios of the observed and predicted concentration between 90 and 150 mins after administration were < 1 (table 2), and this was significant at 120 mins (ANOVA, P < 0.005). The shape of the curve obtained by the final residuals superposed on the second exponential phase, showing an early peak, was strongly suggestive of a second influx of platinum in the plasma compartment during this phase. Because of this, no justification could be found for a straightforward use of the NLIN model. Therefore, the CSTRIP method was used as described under the Method of Data Analysis section. With this approach the basic pharmacokinetic parameters were calculated without assumptions about the character of the intermediate phase (table 1). From the NLIN model it could be deduced that the elimination phase was unaffected by the intermediate phase from Day 1, while the interval 0–15 mins for the calculation of α-half-life was based on maximal correlation coefficients. As expected, an excellent agreement was found between B and β-half-life calculated by CSTRIP and C and γ-half-life calculated by NLIN. The α-half-lives calculated by CSTRIP are only slightly higher than the values found with NLIN because
of the influence of the intermediate phase. The intermediate part of the curve is obtained by subtracting the extrapolated CSTRIP values of the α- and β-phases (C<sub>α</sub>, C<sub>β</sub>) from the levels measured during the first 24 hrs after administration (C<sub>t</sub>). Figure 2 shows C<sub>t</sub>-C<sub>α</sub>-C<sub>β</sub> versus time for all patients. Similar patterns were obtained irrespective of the original shape of the total platinum curve. Peak values of C<sub>t</sub>-C<sub>α</sub>-C<sub>β</sub> were reached between 0.5 and 4 hrs and ranged between 0.24 and 1.1 μg of Pt/ml of plasma. Again, the appearance of peak values suggested a second influx which, together with the duration of the intermediate phase (about 24 hrs), is an argument in favor of the existence of an EHC. The CSTRIP approach also allowed an estimation of the percentage of the dose contributing to this EHC, ie, from the ratio of the areas under the curve C<sub>t</sub>-C<sub>α</sub>-C<sub>β</sub> versus time (AUC<sub>0-24 hr</sub>) and C<sub>t</sub> versus time (AUC<sub>t</sub>). The values obtained ranged from 0.5% to 2.3% (table 1).

In four patients blood samples were obtained for 18 days or longer. NLIN analysis revealed four exponential terms to best fit the total-platinum concentration curves over this observation period. Intercepts, half-life values for the different phases, and standard deviation of observations are summarized in table 3. The terminal half-life in these patients indicates that the rate of elimination is not constant but decreases with time.

Free-platinum concentrations decayed in a biphasic manner. The NLIN fit revealed a half-life of the initial phase of 9.7 mins (range, 9.5–9.8; n = 3), and a mean half-life of the second phase of 40.4 mins (range, 37.5–42.0). Free-platinum concentrations were determined in Patients 1–3, all receiving 100 mg/m<sup>2</sup> of cisplatin. In these patients free-platinum concentrations reached the analytic detection limit 3 hrs after administration. Before that time (90–150 mins after administration), plateau levels of platinum in rbc's were reached (range, 0.51–0.58 μg of Pt/ml). Platinum concentrations in rbc's were followed for 21 and 15 days in Patients 2 and 3, respectively. The decay curves of platinum concentrations in rbc's were best fitted with NLIN by two exponential terms, revealing initial half-life values of 13 and 34 hrs in Patients 2 and 3, respectively, and a half-life value for the second phase of 42 days for Patient 2 and 164 days (due to an outlying concentration on Day 4) for Patient 3. Using linear least-squares analysis, half-life values calculated over the time interval Days 5–15 were 36 and 47 days for Patients 2 and 3, respectively.

Figure 3 illustrates the decay of the platinum concentrations in plasma, plasma ultrafiltrate, and rbc's in one patient (No. 2).

Cumulative urinary excretion of platinum in Patients 1–7 was 24.4% ± 4.6% after 6 hrs. This slowly increased to 41.5% ± 4.7% after 6 days. In Patient 9, cumulative urinary excretion did not differ from that found in the main group of patients. However, in Patient 10 this was reduced, especially during the first 6 hrs (13.9%). After

<table>
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<th>Patient No.</th>
<th>Time-point of measurement (mins)</th>
<th>Ratio of observed and predicted concentrations between 30 and 1440 mins with a triexponential NLIN analysis of the curve for the first 5 days</th>
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<td></td>
<td>30</td>
<td>60</td>
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<td></td>
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</tr>
<tr>
<td></td>
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</tr>
<tr>
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<td></td>
<td>0.978</td>
<td>1.031</td>
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<tr>
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<td>1.063</td>
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the first day the percent increase was in the same range as that found in the other patients.

**In Vitro Observations**

After addition of cisplatin to the isolated plasma and rbc's of Patients 2 and 3, a biphasic decline of the free-platinum concentrations was observed. This is illustrated in figure 3 for Patient 2. Mean half-life values of the initial phase for binding to plasma proteins and rbc's was 72 and 122.4 mins, respectively. For the second phase of binding to plasma proteins this value was 109.7 for Patient 2 and infinite for Patient 3, while the mean half-life value of the second phase for binding to rbc's was 54.5 hrs (range, 52.6-56.4). After incubation for 24 hrs, the mean value for binding to plasma proteins was 96% and to rbc's was 57%.

Studies on the release of platinum from plasma preincubated with cisplatin for 24 hrs revealed only a 5% loss from the platinum-containing half-cell in 8 days. This indicates that cisplatin was almost irreversibly bound to plasma proteins. Exposure of platinum-loaded rbc's to saline also showed that the binding to rbc's is irreversible.

**DISCUSSION**

NLIN curve-fitting has generally been accepted for an accurate computation of the parameters of multiple expo-
TABLE 3.—Values of pharmacokinetic parameters obtained by NLIN analysis of concentration-time curves up to the 36th day

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Observation period (days)</th>
<th>Intercept (µg/ml) A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>Half-life* ( \alpha ) (mins)</th>
<th>( \beta ) (hrs)</th>
<th>( \gamma ) (days)</th>
<th>( \infty ) (days)</th>
<th>SD of observations (%)</th>
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<tr>
<td>4</td>
<td>36</td>
<td>6.25</td>
<td>0.75</td>
<td>1.05</td>
<td>0.63</td>
<td>19.2</td>
<td>1952.1</td>
<td>5.2</td>
<td>15.9</td>
<td>5.85</td>
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<td>8</td>
<td>18</td>
<td>1.97</td>
<td>2.48</td>
<td>0.51</td>
<td>0.83</td>
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<td>1.9</td>
<td>32.9</td>
<td>1.1</td>
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<tr>
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<td>21</td>
<td>1.45</td>
<td>0.27</td>
<td>0.29</td>
<td>0.38</td>
<td>22.9</td>
<td>357.5</td>
<td>3.6</td>
<td>15.3</td>
<td>6.66</td>
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*Half-life = \( \frac{0.693}{\text{slope}} \)

nential functions (31). With this approach we found an optimal fit with three exponential terms for the concentration-time curves up to Day 5, and at least four exponential terms were found when total-platinum concentration curves were analyzed up to at least 18 days. Accurate comparison of elimination half-lives with those reported by others is hindered by the strong dependence on the duration of the period during which platinum concentrations are measured. However, our observations are in agreement with those of other investigators, who also reported the presence of three or more compartments when the measurements were performed for a longer period (11,13,28). The increase of half-life with time may be explained by the appearance of biotransformation products (32,33), an irreversible binding of platinum species to plasma proteins (33), relating half-lives to the turnover rates of plasma proteins, and the existence of deep compartments. Long half-lives due to the presence of deep compartments mean that, in contrast to the plasma compartment, accumulation of platinum may occur in these

**µg Pt/µl**

![Graph](image)

**Figure 3**—Semilogarithmic plots of the platinum concentrations in plasma in vivo (●-●), in plasma ultrafiltrate in vivo (x-x), in rbc's in vivo (○-○), in plasma ultrafiltrate in vitro (■-■), and in rbc's in vitro (▲-▲) vs time in Patient 2.
tissue compartments with an increasing number of cycles (34). This statement is affirmed by organ distribution studies in dogs (35,36), showing significant platinum levels in tissues even 2 months after a single administration of cisplatin (35). The increasing half-life also indicates that the volumes of distribution mentioned in table 1 and calculated from the intercept of the platinum concentrations during Days 1-5 are too low. Nevertheless, the values retain their meaning as an operational volume of distribution.

Because of the irreversible binding of cisplatin to proteins, the V_p of platinum should be placed in a different perspective. In the first place, V_p should be calculated for the unbound drug. Our in vitro studies revealed that 96% of cisplatin is bound to plasma proteins after 24 hrs. This means that the V_D of free-platinum species (V_D,free) is at least 25 times greater than that calculated for total platinum. A V_D,free of about 1600 L indicates that distribution is not restricted to intra- and extra-cellular fluids but also extends to peripheral compartments, where storage may occur. This is in agreement with the distribution studies in dogs, as earlier mentioned, and is also consistent with the incomplete recovery of platinum in human urine.

Excretion of platinum via the urine is the major pathway of excretion; however, biliary excretion of platinum has also been demonstrated in a patient with a permanent T tube (23). Maximum platinum concentrations in the bile of that patient were reached 1 hr after iv bolus injection of cisplatin and then dropped to undetectable levels at 5 hrs. Studies with radiolabeled cisplatin have indicated limited fecal excretion (10,24), and in one of these studies the presence of an EHC was suggested (10). The manifestation of secondary peaks in the declining concentration-time curve in plasma at 3-4 hrs in six of our ten patients and the deviation of the observed concentrations from the second exponential term obtained with the NLIN fit, together with data from the literature, suggest the presence of an EHC (37). Secondary peaks have also been observed by others (21,22).

Because of these indications, we did not restrict ourselves to the overall NLIN three-exponential fit with a listing of the residuals in the second phase, but tried to isolate the results of the second influx (C_p - C_p* - C_p**) by using the described CSTRIP method. This approach also allowed estimation of the extent of EHC.

The biphasic decline of free-platinum concentrations after rapid infusions is in agreement with the data reported by Patton et al (17) and Belt et al (18). In their studies the initial phase was not as pronounced as in our study because of wider time intervals (17) or lack of early measurements after administration (18). For that reason only the terminal half-lives are in very good agreement. It is self-evident that terminal half-life in our study will be longer than that found in studies with a monoexponential approach (25,29). Half-life of free-platinum species is determined by a combination of protein binding, elimination, and transport to tissues. In addition, the terminal half-life might also be influenced by re-entry of platinum into the plasma compartment and metabolism of the original cisplatin (32).

Uptake of platinum into rbc's was very rapid and maximum levels were reached within the period of detectable concentrations of free platinum. The mean maximum platinum level in rbc's (0.54 μg of Pt/ml) was lower than the mean level of platinum bound to proteins at the same time (1.75 μg of Pt/ml). This observation can be clarified by the in vitro experiments in which the uptake of platinum by rbc's was much slower than the binding of platinum to the plasma proteins. The in vitro experiment also showed that after 24 hrs of incubation the concentrations in rbc's and supernatant are almost equal, which indicates the absence of an active transport mechanism and a lack of abundant binding sites in the rbc's. The long final half-life value of platinum in rbc's in vivo is in accordance with the irreversible binding of platinum to rbc's, as postulated from our in vitro studies. The initial rather rapid decrease in rbc platinum concentration needs further elucidation. Our data do not exclude a cisplatin-induced breakdown or a slow release of platinum from rbc's in vivo (38,39).

Patients 8-10 did not differ notably from the other patients as to total-platinum kinetics, but in Patient 10, who had renal impairment, the initial urinary platinum excretion was reduced. Therefore, further studies on free-platinum kinetics should be performed in patients with subnormal renal function, since the findings might indicate the extent to which cisplatin regimens should be adjusted for this group of patients.

It can be concluded that although NLIN has the best features for fitting concentration-time curves, details indicating phenomena such as an EHC may be smoothed away. Extensive sampling, as was done in our study, and the use of CSTRIP allowed an estimation of the EHC of cisplatin.

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