Pharmacokinetics of Carboplatin After IV Administration\textsuperscript{1,2}

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Pharmacokinetics of the cisplatin analog carboplatin were studied in ovarian cancer patients who received short-term IV infusions of 290–370 mg/m\textsuperscript{2}. Platinum (Pt) was determined by atomic absorption spectrometry in plasma ultrafiltrate up to 24 hours and in plasma and urine up to 5 days following infusion. Carboplatin was determined in plasma ultrafiltrate and in urine by high-performance liquid chromatography with electrochemical detection. The final half-life of total Pt in plasma was 5.8 ± 1.6 days. Pharmacokinetics of carboplatin and ultrafilterable Pt (free Pt) were similar with respect to \( \alpha \)-half-life (16 ± 6 and 23 ± 8 mins), \( \beta \)-half-life (118 ± 15 and 120 ± 11 mins), area under curve/dose (18 ± 5 and 17 ± 4 min/m\textsuperscript{2}/L), total-body clearance (101 ± 21 and 107 ± 19 ml/min), and volume of distribution \( V_{\text{ss}} \) (9.9 ± 1.3 and 10.0 ± 1.4 L/m\textsuperscript{2}). After 6 hours the cumulative urinary excretion of carboplatin and Pt was 41% ± 14% and 68% ± 7% of the dose, respectively. After 5 days the cumulative urinary excretion of Pt was 84% ± 6%. Renal and metabolic clearances of free Pt from plasma were 81 ± 17 and 26 ± 11 ml/minute, respectively. The first-order rate constant for metabolic elimination of free Pt (\( K_{M} = \text{CL}_{M}/V_{\text{ss}} \)) was 1.5 × 10\textsuperscript{-3} ± 0.6 × 10\textsuperscript{-3} min\textsuperscript{-1}, which is ten times lower than the value calculated from literature data for cisplatin (15 × 10\textsuperscript{-3} ± 1 × 10\textsuperscript{-3} min\textsuperscript{-1}). This means that the overall in vivo reactivity of carboplatin is ten times lower than that of cisplatin. [Cancer Treat Rep 71:1231–1237, 1987]

Carboplatin, an analog of the antitumor drug cisplatin, has shown appreciable activity against ovarian cancer (1,2). It is less nephrotoxic, neurotoxic, and emetogenic than cisplatin (1,3). Carboplatin-induced myelosuppression is dose-limiting and the maximum tolerated dose (MTD) has been estimated at 300–500 mg/m\textsuperscript{2} in previous phase I trials (1,3). Because of its favorable toxicity profile, carboplatin was and still is evaluated extensively in clinical studies exploring its antitumor activity in comparison with cisplatin (3–7). Comparison with cisplatin was also made in preclinical studies (8–10) and in in vitro studies investigating cytotoxicity and interaction with DNA (11,12). The latter studies revealed that equal amounts of platinum (Pt)-DNA binding induced by different amounts of cisplatin and carboplatin produced equal cytotoxicity.

Pharmacokinetics of cisplatin have been studied extensively (13–17). Comparison of the pharmacokinetics of carboplatin with those of cisplatin will contribute to a better understanding of its therapeutic and toxic effects. So far, pharmacokinetic studies were performed during phase I trials of carboplatin revealing linear pharmacokinetics of Pt (18–22). In one study (21) the original drug was also measured but the limited time interval (4 hours after administration) precluded a proper calculation of pharmacokinetic parameters. For the same reason the final elimination phase of total Pt in plasma has not yet been determined. Patients in the mentioned reports received a wide range of doses and their renal function varied widely. Therefore, the purpose of this study was to assess the pharmacokinetics of carboplatin, ultrafilterable Pt (free Pt), and total Pt in plasma, rbcs, and urine up to 5 days after a short-term IV infusion of carboplatin in patients with advanced ovarian cancer who had normal renal function.

**PATIENTS AND METHODS**

**Patients**

Seven patients with advanced ovarian carcinoma were entered in the study. All patients but one received carboplatin as part of a combination therapy including doxorubicin (given on the same day as carboplatin), hexamethylmelamine, and cyclophosphamide (both given orally from Day 15 to Day 28). Two patients (Nos. 1 and 2; table 1) had never received Pt compounds. All

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patients had normal kidney function (creatinine clearance > 60 ml/minute) except one (No. 3; creatinine clearance, 52 ml/minute), and all had normal liver function. Two patients (Nos. 3 and 4) had malignant effusion. The median age was 55 years (range, 45–66). Vials of lyophilized carboplatin were obtained from Bristol-Myers (Weesp, The Netherlands). The contents were reconstituted with water for injections to obtain a concentration of 10 mg/ml. The appropriate amount was diluted with 5% glucose to 250 ml. This volume was administered with a constant infusion rate in 30–37 minutes (dose range, 290–370 mg/m²).

Sampling

Blood samples (5 ml) were collected in heparinized tubes prior to, half-way through, and at the end of infusion, as well as at 10, 20, 30, 60, 90, 120, 150, 180, 240, 300, 360, and 540 minutes and 24, 48, 72, 96, and 120 hours following the infusion. Samples were processed immediately after collection. Blood was centrifuged and two portions of 1 ml of plasma were ultrafiltrated by MPS-1 systems provided with YMT filters (cutoff, 30,000 daltons) (Amicon, Oosterhout, The Netherlands) (23). The remaining plasma (for total Pt analysis) and both plasma ultrafiltrate samples (for free Pt and carboplatin analyses, respectively) were immediately frozen on dry ice. Rbc's were washed twice with an equal volume of normal saline at room temperature. Urine was successively collected up to 2, 4, 6, 12, 24, 48, 72, 96, and 120 hours after the start of infusion. Small portions of the urine collected over the first three time intervals were frozen immediately. All samples were stored at -25°C and thawed just before analysis.

Analysis

Pt concentrations in plasma (total Pt), plasma ultrafiltrate (free Pt), rbc's, and urine were determined by atomic absorption spectrometry according to the method described earlier (17). High-performance liquid chromatography (HPLC) with differential pulse polarographic detection (24) was used to determine the original drug in plasma ultrafiltrate and urine. The limits of detection by this method were 0.1 and 1 μM and the coefficients of variation were 1.5% and 4.7% in plasma ultrafiltrate and urine, respectively.

Stability of Carboplatin

Plasma ultrafiltrate and urine of healthy volunteers were spiked with aqueous carboplatin solutions of 5 mM to obtain a final concentration of 100 μM.

Three portions of spiked plasma ultrafiltrate and urine were incubated at room temperature. Two samples of 0.15 ml were withdrawn from each portion at regular time intervals over an incubation period of 10 days. Carboplatin was analyzed in the samples immediately after withdrawal.

Two other portions of spiked plasma ultrafiltrate and urine were analyzed for carboplatin, divided in five aliquots of 0.4 ml, and frozen at -25°C. Aliquots were thawed and analyzed in duplicate at regular time intervals over a period of 21 weeks. This test was repeated over a storage period of 40 weeks.

Stability of carboplatin in plasma ultrafiltrate was also tested at 37°C by the daily analysis of two samples over a period of 6 days.

Two patients (Nos. 6 and 7) were treated with carboplatin in combination with ifosfamide and mesna. The administration of both ifosfamide and mesna was started at 4 hours after the administration of carboplatin. Therefore, the stability of carboplatin was also tested in aqueous solutions of 50 μM carboplatin in the presence of 0.2 mM dimesna (2,2'-dithiodiethanesulfonate disodium, supplied by Dr. J. Pohl, Asta Werke, Bielefeld, Federal Republic of Germany) at 37°C for 24 hours. The concentrations used were representative of those expected in plasma (25).

Pharmacokinetic Data Analysis

Postinfusion plasma concentration vs time curves were fitted by the computer program NONLIN (26) to a polyexponential equation, C = ∑(Y_i * e^(-λ_i * t)), Each coefficient Y_i was corrected for the infusion time to C_i, (27) by: C_i = (-λ_i * T_i) / (exp(-λ_i * T) - 1). The area-under-the-plasma-concentration-versus-time curve (AUC = ∑(C_i / λ_i), the area-under-the-first-moment curve (AUMC = ∑(C_i / λ_i^2)) and the total-body clearance (CL = D / AUC, D = dose) were calculated from the obtained coefficients and exponents (27, 28). Renal clearance (CLR) was defined as the cumulative urinary excretion (CUE) divided by the AUC, both measured from the start of infusion up to 6 hours after the end of infusion. The AUC (0–6 hours) was calculated by means of the linear trapezoidal rule. The metabolic clearance (CLM) was calculated for carboplatin and free Pt from CLM = CL - CLR. The half-life of total Pt over Days 1–5 was separately determined by the least-squares method.

The volume of distribution at steady-state (Vss) of total Pt was calculated as Vss = D / AUC × AUMC/AUC (27, 28). Vss's of carboplatin and free Pt were calculated according to Collier (29) by Vss = \[ D[f_1 \cdot MRT_1 + f_2 \cdot MRT_2] / AUC \], in which MRT_1 (= AUMC/AUC) and MRT_2 (= 1/λ_1 + 1/λ_2) (29) are the mean residence times (MRT) in the central and peripheral compartments, respectively, and f_1 and f_2 represent the fractions of the administered dose eliminated from each compartment. These fractions were estimated from CLR and CLM. CLR only takes place from the central compartment, while CLM takes place from the central (CLM) and peripheral
(CL_{M,2}) compartments. CL_{M,1} is thought to be due to the same processes as occur in plasma in vitro, i.e., protein binding and molecular degradation of carboplatin. Therefore, CL_{M,1} = k_{in vitro} \times V_c, in which k_{in vitro} represents the in vitro elimination rate constant from plasma of carboplatin and free Pt, respectively, and V_c [= D/\Delta C_t] (28) represents the volume of distribution of the central compartment. This means that clearance from the central compartment CL_t = CL_R + CL_{M,1} and clearance from the peripheral compartment CL_{P} = CL_M - CL_{M,1}. Thus: f_1 = CL_t/CL and f_2 = CL_{P}/CL. The first-order rate constant of metabolic elimination K_M, representing the overall reactivity of the drug towards body constituents (plasma as well as tissue components), was calculated by analogy with the overall first-order rate constant of elimination at steady-state K_{ss} = CL/V_{ss} (30). Thus: K_M = CL_t/V_{ss}.

RESULTS

Stability of Carboplatin

At room temperature carboplatin (100 \mu M) degraded with half-lives of 19.9 and 6.7 days in plasma ultrafiltrate and urine, respectively. This means that no significant loss of carboplatin will occur when sample preparation takes place immediately after withdrawal. Half-lives of carboplatin at -25°C (storage conditions) in plasma ultrafiltrate were 28.6 and 28.0 weeks on two occasions. However, half-lives in urine varied considerably (212 and 32 weeks). These data indicate that samples can be analyzed within a few weeks after collection. The mean pseudo first-order degradation rate constant in plasma ultrafiltrate at -25°C (k_{obs} = 0.0245 week\(^{-1}\)) was used to correct all carboplatin concentrations in plasma ultrafiltrate for degradation during storage. The appreciable difference in stability in urine was probably caused by differences in urine composition. Such differences have also been observed at 37°C (21). Therefore, no correction could be made for degradation in urine.

A half-life of 98 hours was observed for carboplatin in plasma ultrafiltrate at 37°C. During the 6 days of incubation carboplatin never reached a constant concentration, as reported elsewhere (31). No degradation of carboplatin was observed during the 24-hour incubation with dimersa. Thus, chemical interaction in vivo might be excluded. Aqueous stock solutions of carboplatin (1 and 0.1 mM) stored at ambient temperature protected from light did not show any decrease in concentration up to at least 1 month.

Clinical Pharmacokinetics

Concentration versus time curves of carboplatin and free Pt in plasma ultrafiltrate and total Pt in plasma as well as Pt in rbc's from a representative patient receiving a short-term infusion of carboplatin are shown in figure 1. No secondary peaks in any of these curves were noticed. Concentration-time curves of carboplatin and free Pt were quite similar in all patients for the first 9 hours. Thereafter, both curves diverged; i.e., the concentration-time curve of carboplatin showed a faster drop than that of free Pt. Carboplatin and free Pt could be measured in plasma ultrafiltrate for at least 9 hours.

Peak concentrations and basic pharmacokinetic parameters of individual patients as calculated by non-weighted NONLIN analysis are shown in table 1. Carboplatin and free Pt concentration-time curves were best fitted by two exponential equations. In contrast, all total Pt concentration-time curves declined with three exponential terms. The coefficient of determination r^2 (92) was > 0.996 for all curves.
Mean values of common pharmacokinetic parameters are shown in table 2. Apart from the CUE, all parameters for carboplatin and free Pt were essentially the same. Initial half-lives of total Pt were comparable to those of carboplatin and free Pt. A long terminal half-life of 5.8 ± 1.6 days was separately calculated for total Pt over the discrete time interval of Days 1-5 by means of the least-squares method. This value was somewhat higher than the NONLIN value listed in table 2. The long terminal half-life resulted in high AUC values. Total-body clearance was much lower for total Pt than for free Pt and carboplatin. The high value of Vm for total Pt indicates that an appreciable amount of Pt is bound to the tissues. Sixty percent of the Pt excreted in urine over the first 6 hours after administration consisted of carboplatin.

Table 3 shows the pharmacokinetic parameters related to the clearance of carboplatin in comparison to cisplatin. Total-body clearance of free Pt and carboplatin were about the same. The CLB of free Pt was comparable with the mean creatinine clearance of 73 ± 18 ml/minute as measured the day before the start of therapy, indicating that CLB will principally take place by glomerular filtration, as has been observed before (21,22). CLB was lower for carboplatin than for free Pt, due to metabolic conversions of carboplatin. The overall CLM of carboplatin was about twice that of free Pt. The CLM of carboplatin and free Pt from the central compartment as estimated from their in vitro disappearance rates in plasma [0.0004 min⁻¹ (21) and 0.00024

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**Table 1.** Basic pharmacokinetic data of carboplatin in 7 patients as calculated by NONLIN

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<td>Dose</td>
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<td>343</td>
<td>290</td>
<td>352</td>
<td>349</td>
<td>301</td>
<td>299</td>
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<tr>
<td>μmol/L</td>
<td>1456</td>
<td>1617</td>
<td>1213</td>
<td>1415</td>
<td>1429</td>
<td>1348</td>
<td>1348</td>
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<td>Carboplatin</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;peak&lt;/sub&gt;(μM)</td>
<td>129</td>
<td>102</td>
<td>140</td>
<td>123</td>
<td>125</td>
<td>84</td>
<td>90</td>
</tr>
<tr>
<td>C&lt;sub&gt;1&lt;/sub&gt;(μM)</td>
<td>111</td>
<td>39</td>
<td>100</td>
<td>117</td>
<td>96</td>
<td>57</td>
<td>48</td>
</tr>
<tr>
<td>λ&lt;sub&gt;1&lt;/sub&gt;(×10&lt;sup&gt;-3&lt;/sup&gt; min⁻¹)</td>
<td>31.3</td>
<td>56.2</td>
<td>35.9</td>
<td>66.3</td>
<td>50.2</td>
<td>64.1</td>
<td>27.1</td>
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<tr>
<td>C&lt;sub&gt;2&lt;/sub&gt;(μM)</td>
<td>74</td>
<td>92</td>
<td>96</td>
<td>90</td>
<td>84</td>
<td>71</td>
<td>64</td>
</tr>
<tr>
<td>λ&lt;sub&gt;2&lt;/sub&gt;(×10&lt;sup&gt;-3&lt;/sup&gt; min⁻¹)</td>
<td>6.59</td>
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<td>5.19</td>
<td>5.27</td>
<td>5.11</td>
<td>6.62</td>
<td>6.43</td>
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<tr>
<td>Free Pt</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;peak&lt;/sub&gt;(μM)</td>
<td>134</td>
<td>109</td>
<td>124</td>
<td>116</td>
<td>110</td>
<td>84</td>
<td>90</td>
</tr>
<tr>
<td>C&lt;sub&gt;1&lt;/sub&gt;(μM)</td>
<td>118</td>
<td>43</td>
<td>71</td>
<td>117</td>
<td>72</td>
<td>50</td>
<td>58</td>
</tr>
<tr>
<td>λ&lt;sub&gt;1&lt;/sub&gt;(×10&lt;sup&gt;-3&lt;/sup&gt; min⁻¹)</td>
<td>27.4</td>
<td>23.3</td>
<td>25.5</td>
<td>60.1</td>
<td>45.6</td>
<td>22.7</td>
<td>37.9</td>
</tr>
<tr>
<td>C&lt;sub&gt;2&lt;/sub&gt;(μM)</td>
<td>65</td>
<td>84</td>
<td>85</td>
<td>78</td>
<td>78</td>
<td>51</td>
<td>61</td>
</tr>
<tr>
<td>λ&lt;sub&gt;2&lt;/sub&gt;(×10&lt;sup&gt;-3&lt;/sup&gt; min⁻¹)</td>
<td>6.50</td>
<td>6.29</td>
<td>5.29</td>
<td>5.32</td>
<td>5.28</td>
<td>5.56</td>
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<tr>
<td>Total Pt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;peak&lt;/sub&gt;(μM)</td>
<td>125</td>
<td>113</td>
<td>128</td>
<td>103</td>
<td>106</td>
<td>90</td>
<td>93</td>
</tr>
<tr>
<td>C&lt;sub&gt;1&lt;/sub&gt;(μM)</td>
<td>106</td>
<td>55</td>
<td>76</td>
<td>80</td>
<td>92</td>
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<td>λ&lt;sub&gt;1&lt;/sub&gt;(×10&lt;sup&gt;-3&lt;/sup&gt; min⁻¹)</td>
<td>20.3</td>
<td>22.8</td>
<td>29.2</td>
<td>46.7</td>
<td>82.9</td>
<td>49.9</td>
<td>22.9</td>
</tr>
<tr>
<td>C&lt;sub&gt;2&lt;/sub&gt;(μM)</td>
<td>49</td>
<td>75</td>
<td>74</td>
<td>65</td>
<td>77</td>
<td>70</td>
<td>54</td>
</tr>
<tr>
<td>λ&lt;sub&gt;2&lt;/sub&gt;(×10&lt;sup&gt;-3&lt;/sup&gt; min⁻¹)</td>
<td>5.80</td>
<td>6.66</td>
<td>5.40</td>
<td>5.17</td>
<td>6.65</td>
<td>7.00</td>
<td>5.65</td>
</tr>
<tr>
<td>C&lt;sub&gt;3&lt;/sub&gt;(μM)</td>
<td>4.6</td>
<td>4.6</td>
<td>12.5</td>
<td>6.1</td>
<td>7.1</td>
<td>5.6</td>
<td>4.5</td>
</tr>
<tr>
<td>λ&lt;sub&gt;3&lt;/sub&gt;(×10&lt;sup&gt;-3&lt;/sup&gt; min⁻¹)</td>
<td>0.69</td>
<td>0.84</td>
<td>0.99</td>
<td>1.31</td>
<td>1.62</td>
<td>1.38</td>
<td>0.75</td>
</tr>
</tbody>
</table>

*<sub>C</sub>peak = observed peak concentration. Coefficients (C<sub>1</sub>, C<sub>2</sub>, and C<sub>3</sub>) were corrected for the infusion time.

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**Table 2.** Pharmacokinetic parameters obtained in 7 patients after an iv infusion of carboplatin given over 30 mins

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Carboplatin</th>
<th>Free Pt</th>
<th>Total Pt</th>
</tr>
</thead>
<tbody>
<tr>
<td>t½α(mins)</td>
<td>16 ± 6</td>
<td>23 ± 8</td>
<td>22 ± 10</td>
</tr>
<tr>
<td>t½β(mins)</td>
<td>118 ± 15</td>
<td>120 ± 11</td>
<td>116 ± 14</td>
</tr>
<tr>
<td>t½γ(mins)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>AUC/D(min·m³/L)</td>
<td>18 ± 5</td>
<td>17 ± 4</td>
<td>83 ± 32</td>
</tr>
<tr>
<td>CL(ml/min·m²)</td>
<td>58 ± 12</td>
<td>61 ± 11</td>
<td>13 ± 3</td>
</tr>
<tr>
<td>Vm(L/m²)</td>
<td>9.8 ± 1.3</td>
<td>10.0 ± 1.4</td>
<td>103 ± 32</td>
</tr>
<tr>
<td>CUE(0-6hrs) %D</td>
<td>41 ± 14</td>
<td>68 ± 7</td>
<td>68 ± 7</td>
</tr>
<tr>
<td>CUE(0-24hrs) %D</td>
<td>—</td>
<td>77 ± 5</td>
<td>77 ± 5</td>
</tr>
<tr>
<td>CUE(0-5days) %D</td>
<td>—</td>
<td>84 ± 6</td>
<td>84 ± 6</td>
</tr>
</tbody>
</table>

*Values = mean ± SD.

†n = 5.

‡n = 3.

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**Table 3.** Pharmacokinetic parameters related to the clearance of carboplatin in comparison to cisplatin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Carboplatin</th>
<th>Free Pt</th>
<th>Cisplatin (free Pt)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL(ml/min)</td>
<td>101 ± 21</td>
<td>107 ± 19</td>
<td>354 ± 33</td>
</tr>
<tr>
<td>CLB(ml/min)</td>
<td>44 ± 16</td>
<td>81 ± 17</td>
<td>74 ± 29</td>
</tr>
<tr>
<td>CL%d(ml/min)</td>
<td>57 ± 24</td>
<td>26 ± 11</td>
<td>281 ± 19</td>
</tr>
<tr>
<td>Vm(L)</td>
<td>17 ± 2</td>
<td>17 ± 2</td>
<td>19 ± 2</td>
</tr>
<tr>
<td>KM(×10⁻³ min⁻¹)</td>
<td>3.3 ± 1</td>
<td>1.5 ± 0.6</td>
<td>15 ± 1</td>
</tr>
</tbody>
</table>

*Values = mean ± SD. All values are normalized to 1.73 m² of body surface area.
†Derived from data of Vermorken et al (16,17); n = 3.
(23 min⁻¹) and Vₘ (9 ± 3 and 10 ± 3 L) were 3.6 and 2.4 ml/minute, respectively. With these values for CLₘ, f₁ and f₂ were calculated to be 0.47 and 0.53 for carboplatin and 0.78 and 0.22 for free Pt, respectively. These f values were used to calculate the Vₘ of carboplatin and free Pt (table 3).

For comparison, pharmacokinetic data of free Pt originating from cisplatin, as calculated from the data of Vermorken et al (16,17), are shown in table 3. Total-body clearance of free Pt originating from cisplatin was much higher than that from carboplatin. The CLₘ of free Pt from cisplatin, as calculated from the AUCs and CUEs over the first hour after starting the short-term (7 minutes) infusions (n = 3), were similar to that of carboplatin. The overall CLₘ of free Pt from cisplatin was much higher than that from carboplatin. The CLₘ of free Pt from the central compartment was 71 ml/minute as calculated from the in vitro plasma degradation rate constant of 0.0068 min⁻¹ (23) and a mean Vₘ of 10.5 L. Consequently, f₁ and f₂ were 0.41 and 0.59, respectively. The resulting Vₘ of free Pt from cisplatin was similar to that from carboplatin. Finally, the metabolic rate constant Kₘ was much higher for free Pt originating from cisplatin than from carboplatin, indicating that in vivo carboplatin is a more stable compound than cisplatin.

Pt was taken up in rbc's and 66% ± 8% of the maximum concentration was reached after 60 minutes. Maximum levels of 2.5 ± 0.4 μM were reached at about 6 hours following infusion (median, 360 minutes; range, 240-540). At that time free Pt levels in plasma were still about three times higher than in rbc's. At the maximum concentration about 0.4% of the dose was present in rbc's. The Pt concentration in rbc's decayed monoexponentially, with a half-life of 12 ± 1 day as measured over Days 1-5.

DISCUSSION

The increasing clinical use of carboplatin as an alternative for cisplatin warrants detailed pharmacokinetic investigation. This implies determination of the original Pt complex and Pt concentrations in plasma for a period of time long enough to estimate the final elimination rate constants. Our sensitive and selective HPLC method (24) was capable of determining carboplatin for at least six final half-life times. Total Pt in plasma was determined up to 5 days following infusion, allowing a reliable fit of a triexponential equation for the concentration-time curves.

The concentration-time curves of total Pt in plasma coincided with those of free Pt and carboplatin for about 6 hours after administration, indicating that, in contrast to cisplatin, carboplatin binds only slowly to plasma proteins. This is in accordance with earlier reports (21) and in vitro observations (23,31,33). The slow protein binding is also reflected by a high cumulative urinary excretion of Pt, being 68% of the dose over the first 6 hours, compared to 24% of the dose for cisplatin over the same time interval (16).

No signs of enterohepatic recycling, as described for cisplatin (16,17), were observed. Biliary excretion of Pt may be lower after carboplatin than after cisplatin, as was also observed in rats (34), although in dogs the amount of Pt involved in enterohepatic recycling was higher after carboplatin than after the administration of cisplatin, ioproplatin, spiroplatin, or JM-40 (35). Also, one clinical study reported secondary peaks in total and free Pt concentration-time curves (19). No definite conclusion can be drawn from these contradictory observations.

Total Pt concentrations in plasma at 24 hours after administration of 350 mg/m² of carboplatin (6 ± 3 μM) were similar to those obtained after 100 mg/m² of cisplatin (8 μM (16,17)). Furthermore, the total amount of Pt present in the body after 24 hours, as calculated from the CUE over 0-24 hours, was 23% D and 72% D (17) for carboplatin and cisplatin, respectively. These amounts correspond with 0.22 and 0.24 μmol/m² of carboplatin and cisplatin, respectively. This observation is in agreement with tissue levels at 24 hours after administration of the MTD in nude mice as measured by Boven et al (10). This means that the amounts of both drugs reacted with plasma proteins and tumor and tissues are about the same at the MTD. Furthermore, the final half-life of total Pt, as measured by the least-squares method over the first 5 days, corresponded very well with the final half-life observed after short-term infusion of cisplatin (t₁/₂, Days 1-5 = 5.3 days) (16). This suggests that similar Pt-protein reaction products were formed.

The resemblance of carboplatin and free Pt with respect to their half-lives, MRT, AUC, CL, and Vₘ (table 2) indicates a slow metabolic conversion of carboplatin to species with a molecular weight < 30,000. Although the plasma concentrations of carboplatin and free Pt were almost equal, the urinary excretion (0-6 hours) of carboplatin was lower than that of free Pt. This may be caused by a lower glomerular filtration of carboplatin or by degradation of carboplatin in the bladder during the collection intervals of 2 hours (21).

The difference in carboplatin and free Pt concentrations from 9 hours after administration onwards provides evidence for the presence of low-molecular-weight metabolites, formed either by direct conversion of carboplatin or by degradation of protein-carboplatin complexes. The CLₘ of free Pt (table 3) was in excellent agreement with the value of 23 ml/minute calculated by Calvert et al (3) in a totally different way.

Kₘ of free Pt appeared to be ten times higher for cisplatin than for carboplatin. Therefore, it can be concluded that in vivo cisplatin is about ten times more reactive than carboplatin. This factor of ten is in good agreement with the difference in reactivity towards the strong nucleophile sodium thiosulfate (36). Difference in reactivity was also thought to be the cause of a difference in binding to DNA (11) and cytotoxicity (12). In solutions a 100-fold-higher concentration of carboplatin was needed to reach equal levels of Pt-DNA intrastrand.
crosslinks, which produced equivalent DNA damage after 24 hours of incubation (11). In cell suspensions, however, 20-40-fold more carboplatin than cisplatin was required to produce DNA binding and cytotoxicity to the same extent (11). This decrease in excess of dose may be explained by the fact that a relatively lower amount of cisplatin will reach DNA due to a difference in reactivity to cellular components on their way to the nucleus. Similarly, because even more alternative re- actions of cisplatin will be possible, it can be understood that in vivo the excess of carboplatin needed to induce equal cytotoxicity is about tenfold as reflected by the observed ratio of the AUCs of free Pt in plasma after a dose of 350 and 100 mg/m² of carboplatin and cisplatin, respectively (16,17).

The concentration-time profile of Pt in rbc also indicates a lower reactivity of carboplatin compared to cisplatin. Peak Pt concentrations in rbc were lower than those observed after administration of 100 mg/m² of cisplatin [2.9 ± 0.4 μM (17)], despite the higher dose of carboplatin (350 mg/m²). Peak levels were also reached at later time points.

It can be concluded that pharmacokinetics of carboplatin reflect its lower reactivity compared to cisplatin. By giving higher amounts of carboplatin to cancer patients a comparable extent of reaction with human body constituents may be achieved.

REFERENCES
27. WAGNER JG. Linear pharmacokinetic equations allowing direct calculation of many needed pharmacokinetic parameters from the coefficients and exponents of polynomal equations which have been fitted to the data. J Pharmaceutic Biopharm 4:443-467, 1976.

