DISPOSITION OF [G-3H]PACLITAXEL AND CREMOPHOR EL IN A PATIENT WITH SEVERELY IMPAIRED RENAL FUNCTION

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ABSTRACT:
In the present work, we studied the pharmacokinetics and metabolic disposition of [G-3H]paclitaxel in a female patient with recurrent ovarian cancer and severely impaired renal function (creatinine clearance: 20 ml/min) due to chronic hypertension and prior cisplatin treatment. During six 3-weekly courses of paclitaxel at a dose level of 157.5 mg/m² (viz. a 10% dose reduction), the renal function remained stable. Pharmacokinetic evaluation revealed a reproducible and surprisingly high paclitaxel area under the plasma concentration-time curve of 26.0 ± 1.11 μM·h (mean ± S.D.; n = 6; c.v. = 4.29%), and a terminal disposition half-life of 29 h. Both parameters are substantially increased (~1.5-fold) when compared with kinetic data obtained from patients with normal renal function. The cumulative urinary excretion of the parent drug was consistently low and averaged 1.58 ± 0.417% (± S.D.) of the dose. Total fecal excretion (measured in one course) was 52.9% of the delivered radioactivity, and mainly comprised known mono- and dihydroxylated metabolites, with unchanged paclitaxel accounting for only 6.18%. The plasma area under the plasma concentration-time curve of the paclitaxel vehicle Cremophor EL, which can profoundly alter the kinetics of paclitaxel, was 114.9 ± 5.39 μM·h/ml, and not different from historic data in patients with normal or mild renal dysfunction. Urinary excretion of Cremophor EL was less than 0.1% of the total amount administered. These data indicate that the substantial increase in systemic exposure of the patient to paclitaxel relates to decreased renal metabolism and/or urinary elimination of polar radioactive species, most likely lacking an intact taxane ring fragment.

The antineoplastic agent paclitaxel has been known as a highly effective chemotherapeutic agent in platinum-refractory ovarian cancer since 1989 (McGuire et al., 1989; Ozols, 1998; Wiseman and Spencer, 1998). Fifteen to thirty percent of patients with cisplatin-resistant disease respond to paclitaxel treatment, and in up to 7% of the cases complete remissions can be achieved. These response rates are even higher in patients with tumors still sensitive to platinum-containing chemotherapy. Treatment with paclitaxel at a dose of 175 mg/m² infused over 3 h once every 3 weeks is a widely accepted and registered regimen in this indication (Ozols, 1998).

The clinical pharmacokinetic behavior of paclitaxel is characterized by a distinct nonlinear disposition profile (Sonnichsen and Relling, 1994; Gianni et al., 1995), with renal elimination pathways of the parent drug accounting for less than 15% of the dose (Rowsksy, 1995; Walle et al., 1995). The primary routes of paclitaxel elimination consist of successive hydroxylation reactions and biliary and intestinal secretion of the parent drug and its metabolic products (Monsarrat et al., 1993; Sparreboom et al., 1997). The major metabolic products identified in humans correspond to two monohydroxylated compounds with a hydroxyl function on the α-position at C6 of the taxane ring (6α-hydroxypaclitaxel) or on the para-position of the phenyl group at C3’ in the C13 side chain (3’-hydroxypaclitaxel) and 1 dihydroxylated compound (6α,3’-dihydroxypaclitaxel) (Harris et al., 1994a; Sparreboom et al., 1995; Royer et al., 1995). The 6α-hydroxylation has been shown to be catalyzed by cytochrome P-450 3A4 (Harris et al., 1994b; Kumar et al., 1994).

Consistent with the importance of hepatic elimination by the cytochrome P-450 family, a recent clinical study with paclitaxel administered to a large group of patients with liver dysfunction showed a substantial increase in experienced toxicity (Venook et al., 1998). In contrast, published pharmacologic data on paclitaxel in adults with renal failure are very limited and available only in abstract form (Schilder et al., 1994; Fazeny et al., 1995; Conley et al., 1997). In addition, it is noteworthy that there are no data of patients with severe, predialysis renal impairment treated with paclitaxel. In the present report, we describe the pharmacokinetics of paclitaxel and its formulation vehicle Cremophor EL in a patient with recurrent ovarian cancer and severely impaired renal function who was treated with six 3-weekly courses of paclitaxel. In one of the courses, we used [G-3H]-paclitaxel to allow detailed assessment of the elimination routes of paclitaxel and to determine its complete metabolic fate.

Patient, Materials, and Methods

Patient Characteristics and History. The patient studied was a 65-year-old Caucasian female, initially diagnosed at 55 years of age with FIGO (i.e., the International Federation of Gynaecology and Obstetrics) stage 3C poorly

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differentiated serous ovarian cancer. She was also known to have poorly regulated hypertension and chronic, slowly progressive renal insufficiency, presumably due to nephrosclerosis, although a histologic biopsy to prove the diagnosis was never performed. After successful debulking surgery, the patient was treated with six cycles of combination chemotherapy consisting of cisplatin and cyclophosphamide. She remained in complete remission for 7 years, until December 1996, when there was a local relapse. Second line chemotherapy with carboplatin and cyclophosphamide again induced a complete remission; at that time, the creatinine clearance was 30 ml/min. One and a half years later, the patient again relapsed locally, and was simultaneously diagnosed with a metastasis adjacent to the transverse colon in the upper abdomen. The creatinine clearance was decreased to around 20 ml/min, whereas hematopoesis and the results of liver function tests were all normal. It was decided to treat the patient with a 3-weekly schedule of paclitaxel at the recommended dose of 175 mg/m² minus 10% (viz. 157.5 mg/m²) to avoid potential risks related to the critical preterminal renal insufficiency. During therapy, the patient did not use any comedication that might have interfered with paclitaxel disposition. Throughout six courses of treatment, the creatinine clearance remained stable. The courses were very well tolerated without any sign of substantial bone marrow suppression or deterioration of other organ functions. A computer tomographic scan performed after three courses showed a partial response, which was sustained after an additional three cycles.

Chemicals. Paclitaxel powder (batch 484034; purity 98.3% by reversed phase HPLC) and commercially available paclitaxel formulated in a mixture of Cremophor EL and dehydrated ethanol USP (Taxol; 1:1, v/v) were kindly provided by Bristol-Myers Squibb (Woerden, the Netherlands). The internal standard for quantitative paclitaxel analysis, docoltaxel (batch 14RPOC92320; purity 98.0% by reversed phase HPLC), was obtained from Rhone-Poulenc Rorer (Vitry-sur-Seine Cedex, France). Authentic reference standards for 6α-hydroxypaclitaxel, 3′-p-hydroxy-paclitaxel, and 6α,3′-p-dihydroxypaclitaxel were obtained after isolation and purification of patient fecal samples, as described (Sparreboom et al., 1995). Chemical structures of the standards were confirmed by on-line photodiode array detection and fast atom bombardment ionization/mass spectrometry, with the compounds dissolved in methanol added to a glycerol matrix, using a JMS-SX/SX102A Tandem Mass Spectrometer (Jeol, Tokyo, Japan) with a 6-kV xenon atom beam and a 10-kV accelerating voltage. Standards of baccatin III (purity: >95.0%) and 10-deacetyl-baccatin III (purity: >95.0%) from Taxus baccata were purchased from Sigma-Aldrich Chemie (Zwijndrecht, the Netherlands). [2,3H]-Paclitaxel (batch 227-163-0024; radiochemical purity 99.7%) with a specific activity of 2.4 Ci/mmol was supplied by Moravek Biochemicals, Inc. (Brea, CA). The majority of the tritium is in the m- and p-positions of the aromatic rings, with minor amounts in the 10-, 3′-, and 2-positions of the taxane ring system (see Fig. 1). The Cremophor EL reference material was obtained from Sigma Chemical Co. (St. Louis, MO), and Coomassie brilliant blue G-250 was purchased from Bio-Rad Laboratories (Munich, Germany) as a concentrated solution in 85% (w/v) phosphoric acid/95% (v/v) ethanol (2.1, v/v). All other chemicals and reagents used were of reagent grade or better, and originated from Rathburn (Walkerburn, UK). HPLC-grade water was obtained from a Millipore (Milford, MA) Milli-Q-UF system. Ultima Gold scintillation cocktail was purchased from Packard (Meriden, CT).

Treatment and Sampling Schedule. The patient studied received the courses of paclitaxel at a dose level of 175 mg/m² minus 10% (viz. 157.5 mg/m²) by a 3-h i.v. infusion. In the third course, the dosing solution for administration was prepared by adding a stock solution of [2,3H]-Paclitaxel in absolute ethanol USP to unlabelled paclitaxel in Cremophor EL/ethanol (1:1, v/v; 6 mg/ml), and diluting this mixture with an aqueous solution composed of 5.25% (w/v) glucose and 0.9% (w/v) sodium chloride. The final dose solution contained 56.9 ng of [2,3H]-Paclitaxel per ml, 512 μg of unlabeled paclitaxel per ml, and 42.7 μl of Cremophor EL per ml (target dose volume, 308 ml/m²). Blood samples (~5 ml) for pharmacokinetic studies were obtained during all treatment courses in glass hemogard vacutainer tubes with lyophilized sodium heparin (Becton Dickinson, Meylan, France) as anticoagulant, and were obtained at the following time points: immediately before dosing; at 0.5, 1, 1.5, 2, 2.5, and 3 h after start of infusion; and at 5, 15, 30, and 45 min and 1, 2, 4, 6, 8, 12, and 24 h after the end of infusion. Samples were centrifuged at 4000g for 5 min (4°C) to yield the plasma fraction, which was stored frozen at −80°C in polypropylene vials (Eppendorf, Hamburg, Germany). Complete urine and feces collections were obtained for up to 5 days, and were stored immediately at −80°C in polyethylene containers. Aliquots of urine samples were diluted in 10 volumes of drug-free human plasma to prevent continuing degradation of the analytes (Rangel et al., 1994). Weighted feces samples were homogenized individually in 10 volumes of water using five 1-min bursts of an Ultra-Turrax T25 homogenizer (IKA-Labotechnik, Dottingen, Germany) operating at 20,500 rpm. Aliquots of the feces homogenate were diluted with human plasma before additional sample processing as described above for urine.

Drug Measurement. Paclitaxel concentrations in plasma, urine, and feces homogenate were measured by reversed phase HPLC with UV detection after a single solvent extraction, as described (Sparreboom et al., 1998a). Radioactivity in urine and triplicate aliquots of feces homogenate was determined by liquid scintillation counting using Ultima Gold scintillation cocktail, with a Wallac System 1400 counter (Turku, Finland). Each sample was pretreated with a 5-fold volume of acetonitrile by vigorous mixing to remove particulates. Estimates of residual radioactivity in the particulates were determined after digestion with 200 μl of sulfuric acid and neutralization of the solubilization mixture with a 25% (v/v) solution of ammonium hydroxide. All samples were counted until a preset time of 20 min was reached, with quench correction performed by external standardization. The analytical procedure for Cremophor EL in plasma was based on a colorimetric binding assay (Sparreboom et al., 1998b), with modifications as described (Brouwer et al., 1998), using the Coo massie brilliant blue G-250 dye. Cremophor EL concentrations in urine were determined using a modification of the same assay, using 1-ml samples for clean-up and a calibration curve constructed in drug-free urine over a range of 0.01 to 0.2 μl/ml.

Separation and Identification of Metabolites. Paclitaxel metabolites in unextracted urine (~1 ml) and fecal extracts (corresponding to approximately 100 μg of feces) were separated and quantified by HPLC with UV detection or by liquid scintillation counting of collected fractions. The isotropic HPLC system consisted of a constaMetric 3200 solvent delivery system (LDC Analytical, Riviera Beach, FL), a Waters 710plus autosampling device (Milford, MA), a model SP609 column oven (Spark Holland, Meppel, the Netherlands), a SpectraPhysics UV-2000 variable wavelength detector (San Jose, CA), and a FRAC-100 fraction collector equipped with a PSV-50 valve (Pharmacia Biotech, Uppsala, Sweden). Analytes were separated on a stainless steel analytical column (150 × 4.6 mm i.d.) packed with a stationary phase of 5 μm of Inertisil ODS-80A material (GL Science, Tokyo, Japan) supplied with a Lichrodisp 100 PR-18 guard column (4.0 × 0.4 mm; 5-μm particles). The
mobile phase consisted of water/methanol/tetrahydrofuran/ammonium hydroxide (54.5:42.5:2:0.1, v/v/v/v), with the pH adjusted to 6.0 (formic acid). The flow rate of the mobile phase was set at 1.0 ml/min with detection performed simultaneously at 230 and 254 nm, at a column temperature of 60°C. Effluent fractions (1 ml) were collected, and 3H-labeled metabolites were quantified by liquid scintillation counting. In each case, the recovery of radioactivity from the HPLC column was typically >95%. Mass spectra of isolated compounds were obtained from liquid chromatography/dual mass spectrometry analysis using a Finnigan MAT LCQ mass spectrometer (ThermoQuest Co., San Jose, CA) operated with an electrospray ionization probe. Samples were introduced into the interface through a heated nebulizer probe (500°C) using nitrogen as nebulizing gas. A discharge voltage of 3.3 kV was applied to the corona discharge needle to produce a discharge current of 5 μA, with a capillary temperature adjusted to 175°C. The tube lens offset voltage was adjusted to +40 V to maximize sensitivity by balancing desolvation with fragmentation. Mass spectrometry data were collected over m/z 200 to 1000.

Pharmacokinetic Data Analysis. Plasma concentration versus time data were analyzed using the Siphar software package (version 4.0; SIMED, Créteil, France), by determination of slopes and intercepts of the plotted curves with multieponential functions. The program determined initial parameter estimates, and these were improved using an iterative numerical algorithm based on Powell’s method. Model discrimination was assessed by a variety of considerations including visual inspection of the predicted curves, dispersion of residuals, minimization of the sum of weighted squares residuals, and the Akaike and Schwartz information criteria. Final values of the iterated parameters, including drug disposition half-lives (T1/2), area under the plasma concentration-time curve (AUC), and half-life of terminal disposition phase (Vd,ss), were analyzed using the Siphar software package (version 4.0; SIMED, Créteil, France) operated with an electrospray ionization probe. Samples were introduced into the interface through a heated nebulizer probe (500°C) using nitrogen as nebulizing gas. A discharge voltage of 3.3 kV was applied to the corona discharge needle to produce a discharge current of 5 μA, with a capillary temperature adjusted to 175°C. The tube lens offset voltage was adjusted to +40 V to maximize sensitivity by balancing desolvation with fragmentation. Mass spectrometry data were collected over m/z 200 to 1000.

Results

Analytical Methods. To gain a preliminary insight into the composition of the paclitaxel metabolites present in the various biological matrices, samples from the patient were initially analyzed by our HPLC procedure developed for plasma (Sparreboom et al., 1998a). This method was subsequently modified for analysis in feces homogenates, and urine, so that baseline resolution of all the chromatographic peaks observed in samples could be achieved. Using this HPLC system, mean chromatographic run times for known compounds were established using pure reference substances at 3.61 min (10-deacetyl-baccatin III), 5.50 min (baccatin III), 15.0 min (6a,3’-p-dihydroxypaclitaxel), 18.8 min (3’-p-hydroxypaclitaxel), 35.0 min (6a-hydroxypaclitaxel), and 51.8 min (paclitaxel). Structural identification of unknown compounds was based on HPLC data, UV absorption characteristics at 230 nm, and mass spectrometry of isolated peaks relative to reference derivatives. Plasma Disposition. The plasma concentration-time profiles of unchanged paclitaxel were remarkably similar for the six consecutive treatment courses studied. All the profiles were best fitted to a three-compartmental model after zero-order input using the Powell minimization algorithm and weighted least-squares analysis with a weighting factor of 1/Y. The mean plasma pharmacokinetic parameters of paclitaxel, as calculated by this triexponential model are listed in Table 1. Plasma concentrations of paclitaxel decreased rapidly immediately after cessation of the 3-h infusion (Fig. 2A), followed by a more prolonged disposition half-life of ~29 h, which is approximately 1.5-fold higher as compared with data reported previously in patients with normal renal function (Gianni et al., 1995). Similarly, the paclitaxel plasma AUC extrapolated to infinity was very reproducible and achieved surprisingly high values of 26.0 ± 1.11 μM h (mean ± S.D.).

Urinary and Fecal Disposition. The urinary excretion pattern, measured on three consecutive courses, was virtually identical throughout these treatment courses, with 1.58 ± 0.417% of the dose excreted as unchanged drug in the first 24 h after drug administration (Table 2). The mean renal clearance of paclitaxel, defined as the product of the dose-fractio excreted unchanged and total body clearance, was 0.181 ± 0.047 liter/h, indicating that as much as 98% of the overall clearance could be attributed to nonrenal processes. The total cumulative urinary excretion of radiolabeled compounds after [G-3H]paclitaxel administration accounted only for 2.25% of the dose, of which 1.15% constituted metabolic products. Reversed phase HPLC tracings with UV detection and scintillation detection of a urine extract from a urine sample collected during the first 3 h after dosing are presented in Fig. 3. In addition to the parent drug, trace levels of 10-deacetyl-baccatin (MH+ ion at m/z 545) and baccatin III (MH+ ion at m/z 587) could be detected (both accounting for less than 0.01% of the dose), and an unknown prominent radioactive peak early in the solvent front that was reported previously (Walle et al., 1995; Sparreboom et al., 1997).

Data of fecal elimination, obtained only during the third treatment course, indicated that 52.9% of the delivered radioactivity was excreted in the first 24 h, with unchanged paclitaxel accounting for only 6.18%. In fecal extracts, 6α-hydroxy-paclitaxel (MH+ ion at m/z 870; taxane fragment ion at m/z 525) could clearly be distinguished as the predominant species (see Fig. 2A). Using reference derivatives, two of the additional paclitaxel metabolites could be identified as 6α,3’-p-dihydroxy-paclitaxel (MH+ ion at m/z 886) and 3’-p-hydroxy-paclitaxel (MH+ ion at m/z 870; taxane fragment ion at m/z 509). The peak labeled 1 in Fig. 2A showed a molecular ion at m/z 870 and a fragment ion at m/z 509, suggesting an unknown metabolite(s) resulting from a single hydroxylation reaction in the C13 side chain. A second unidentified peak (labeled 4 in Fig. 2A) had an abundant ion at m/z 509, suggesting an unknown metabolite(s) resulting from a single hydroxylation reaction in the C13 side chain.

Cremophor EL Kinetics. Disappearance of the paclitaxel formulation vehicle Cremophor EL from the plasma compartment was characterized by elimination in an apparent biexponential manner (Fig. 2B). The peak plasma concentrations and AUC values of Cremophor EL in the three subsequent cycles, shown in Table 1, were 3.51 ± 0.17 μl/ml (mean ± S.D.) and 114.9 ± 5.39 μl/ml, respec-

| TABLE 1 |

<table>
<thead>
<tr>
<th>Compound</th>
<th>AUC_{0-t}</th>
<th>AUC_{0-∞}</th>
<th>C_{max}</th>
<th>T_{1/2,α}</th>
<th>V_{d,ss}</th>
<th>Cl</th>
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<tr>
<td>Paclitaxel</td>
<td>Mean</td>
<td>20.30</td>
<td>26.18</td>
<td>5.810</td>
<td>23.7</td>
<td>401</td>
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<tr>
<td>S.D.</td>
<td>1.26</td>
<td>1.25</td>
<td>0.745</td>
<td>5.21</td>
<td>54.5</td>
<td>0.55</td>
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<tr>
<td>c.v.</td>
<td>6.21</td>
<td>4.77</td>
<td>12.8</td>
<td>22.0</td>
<td>13.6</td>
<td>4.91</td>
</tr>
<tr>
<td>Cremophor EL</td>
<td>Mean</td>
<td>56.89</td>
<td>114.9</td>
<td>3.51</td>
<td>27.1</td>
<td>7.07</td>
</tr>
<tr>
<td>S.D.</td>
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<td>5.393</td>
<td>0.170</td>
<td>2.97</td>
<td>0.46</td>
<td>0.009</td>
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<tr>
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<td>4.69</td>
<td>4.89</td>
<td>11.0</td>
<td>6.49</td>
<td>4.58</td>
</tr>
</tbody>
</table>

*Abbreviations used are: AUC, area under the plasma concentration-time curve.*
tively, and are consistent with earlier findings obtained from a large cohort of patients treated with paclitaxel at a similar dose of 150 mg/m² (Sparreboom et al., 1998c). The cumulative urinary excretion of Cremophor EL was very low and accounted for 0.08 ± 0.02% (mean ± S.D.) of the administered dose.

Discussion

The administration of paclitaxel to patients with renal insufficiency has been reported previously in five cases and in all, patients were on (long-term) hemodialysis (Schilder et al., 1994; Fazeny et al., 1995; Balat et al., 1996; Conley et al., 1997; Woo et al., 1999). Although paclitaxel pharmacokinetics was determined in some of these patients, the lack of fecal and urinary data precluded a complete analysis of paclitaxel disposition. In contrast to these previous investigations, we evaluated paclitaxel plasma pharmacokinetics during six sequential evaluated courses. Our patient exhibited a quantitatively distinct kinetic profile of paclitaxel, with paclitaxel AUC values and disposition half-lives in plasma approximately 1.5- to 2-fold higher as compared with those reported in patients with normal renal function (Rowinsky, 1995; Gianni et al., 1995). This high paclitaxel AUC value, which was sustained over the six consecutive courses, justifies a dose reduction of paclitaxel in patients with severe predialysis renal impairment although, surprisingly, no major (hematological) toxicity, other than mild fatigue, was observed in this patient.

We have recently shown that Cremophor EL, the formulation vehicle used for i.v. paclitaxel administration, causes a profound concentration-dependent alteration of drug accumulation in erythrocytes by reducing the free drug fraction available for cellular partitioning (Sparreboom et al., 1999). This phenomenon is caused by micellar incorporation of paclitaxel in the systemic circulation and results in increased plasma concentrations and 'artificial' nonlinear disposition (Sparreboom et al., 1996). Because no data were available on Cremophor EL kinetics in patients with renal failure, we speculated that the increased exposure of our patient to paclitaxel, expressed as the AUC in plasma, might have been caused by alteration of Cremophor EL disposition and elimination. However, involvement of Cremophor EL in the observed kinetic behavior of paclitaxel could eventually be ruled out as the plasma clearance and AUC were comparable with those reported previously in a historic control group of patients with normal renal function on a similar treatment schedule (Sparreboom et al., 1998c). Consistent with this observation, we found that urinary excretion of Cremophor EL was very low and accounted for only less than 0.1% of the delivered dose in this patient. This suggests that renal excretion of intact Cremophor EL and its major constituent polyoxyethylene glycerol triricinoleate is not important in the overall elimination of this vehicle substance.

Alternatively, we investigated the possibility that metabolic routes and excretion pathways of paclitaxel itself might have been altered due to the disease state of the patient. This was achieved by the use of radiolabeled paclitaxel in the third treatment course. As demonstrated previously, fecal excretion constituted the main route of excretion, with 52.9% of the administered radioactivity recovered in a 24-h feces
collection period. This is in excellent agreement with earlier data of Walle et al. (1995), who reported that $59.1 \pm 7.3\%$ of the total dose was excreted as extractable radioactivity in five patients with normal organ functions. In line with this study and with our own work characterizing the main hepatic metabolites in patient feces samples (Sparreboom et al., 1995), only approximately 6% of the fecal radioactivity was excreted as unchanged paclitaxel. 6$\alpha$-Hydroxypaclitaxel constituted the major metabolite, with 3$\beta$-hydroxypaclitaxel and 6$\alpha$,3$\beta$-dihydroxypaclitaxel both present as minor biotransformation products, in addition to two unknown compounds. In contrast to fecal data, the cumulative urinary excretion of radiolabeled paclitaxel was significantly different from other published data (Walle et al., 1995); the total urinary excretion of $^3$H-labeled paclitaxel and metabolites accounted for 14.3 $\pm$ 1.4% (range, 11.0–18.7%) of the dose, with the parent drug representing 4.5 $\pm$ 0.5% (range, 3.3–6.2%) versus 2.25% (total radioactivity) and 1.58 $\pm$ 0.42% (paclitaxel), respectively, in our patient. These comparative data seem to indicate that renal elimination of paclitaxel and its metabolites, particularly the large unknown polar constituents, which may represent (part of) the C13 side chain, is markedly impaired, and this may have contributed to the altered pharmacokinetic profile observed in plasma.

In conclusion, we have shown altered plasma pharmacokinetics of paclitaxel in a patient with severely impaired renal function, treated at a 10%-reduced dose during six consecutive courses. Our findings indicate that the substantial increase in systemic exposure of our patient to paclitaxel most likely relates to decreased renal metabolism and/or urinary excretion of unchanged drug or polar radioactive species. These data point to a more prominent role of the kidneys in paclitaxel disposition than previously thought and suggest that additional studies are required to fully appreciate to what extent renal dysfunction can affect paclitaxel pharmacokinetics and pharmacodynamics. Such studies should focus on mechanisms by which any difference observed might be explained.

References


