Quantitative Effect of Gender, Age, Liver Function, and Body Size on the Population Pharmacokinetics of Paclitaxel in Patients with Solid Tumors

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Abstract

Background: The aim of this study was to quantitatively assess the effect of anthropometric and biochemical variables and third-space effusions on paclitaxel pharmacokinetics in solid tumor patients.

Materials and Methods: Plasma concentration-time data of paclitaxel were collected in patients with non–small cell lung cancer (n = 84), ovarian cancer (n = 40), and various solid tumors (n = 44), totaling 168 patients. Paclitaxel was given as a 3-hour infusion (n = 163) at doses ranging from 100 to 250 mg/m², or as a 24-hour infusion (n = 5) at a dose of 135 or 175 mg/m². Data were analyzed using nonlinear mixed-effect modeling.

Results: A three-compartment model with saturable elimination and distribution was used to describe concentration-time data. Male gender and body surface area were positively correlated with maximal elimination capacity of paclitaxel (VMEL); patient age and total bilirubin were negatively correlated with VMEL (P < 0.005 for all correlations). Typically, male patients had a 20% higher VMEL; a 0.2 m² increase of body surface area led to a 9% increase of VMEL; a 10-year increase of patient age led to a 5% decrease of VMEL; and a 10-μmol increase of total bilirubin led to a 14% decrease of VMEL. Third-space effusions were not correlated with paclitaxel pharmacokinetics.

Conclusions: This extended retrospective population analysis showed patient gender to significantly and independently affect paclitaxel distribution and elimination. Body surface area, total bilirubin, and patient age were confirmed to affect paclitaxel elimination. This pharmacokinetic model allowed quantification of the covariate effects on the elimination of paclitaxel and may be used for covariate-adapted paclitaxel dosing.

Paclitaxel formulated in Cremophor EL is regularly administered to patients with non–small cell lung cancer (NSCLC), ovarian cancer, and breast cancer. The pharmacokinetics of paclitaxel were initially believed to be linear, but Sonnichsen and Gianni reported that paclitaxel pharmacokinetics were best described with a two- and three-compartment model, respectively, with saturable elimination and saturable distribution to the tissues (1, 2). Later, the formulation vehicle of paclitaxel, Cremophor EL, was reported to be the cause of the (apparent) nonlinear plasma behavior of paclitaxel, probably by entrapment of paclitaxel into micelles (3–7). Generally, substantial interpatient variability of paclitaxel pharmacokinetic variables has been noted (8).

Hepatic metabolism and biliary excretion are the most important elimination routes of paclitaxel and its metabolites (9). Paclitaxel has been shown to bind extensively to plasma proteins (from 95% to < 97%), with high central (mean = 13.8 L/m²) and steady-state (mean = 182 L/m²) volumes of distribution (10–13). However, data on specific tissue and compartment distribution of paclitaxel in humans following i.v. administration are limited. Paclitaxel concentrations in ascites have been analyzed in single patients, where the concentration of paclitaxel slowly rose over several hours after drug infusion to reach maximum concentrations exceeding paclitaxel plasma concentrations (11, 14). Patients with ovarian cancer and NSCLC often exhibit third-space effusions, and good activity of paclitaxel has repeatedly been shown in Japanese patients with gastric cancer and malignant ascites (15–19). Although third-space effusions are known to impair the elimination of drugs with a small distribution volume, like methotrexate, the quantitative effect of pleural effusions and ascites on paclitaxel pharmacokinetics has not been studied thus far.

The nonlinear pharmacokinetics of paclitaxel have extensively been described (2, 20–23), and population pharmacokinetic models have mostly implemented saturable elimination.
and distribution (8, 24, 25). Furthermore, patients with biochemical evidence of (cholestatic) liver dysfunction (26, 27) or the presence of liver metastases (26, 28) experienced more hematologic and nonhematologic toxicity from paclitaxel. The exposure-toxicity relationship of paclitaxel is not linear but could be described by a threshold model, whereas the time above a paclitaxel plasma concentration of between 0.05 and 0.2 μmol/L was correlated with hematologic toxicity (2, 8, 26, 28, 29). Finally, an exposure-response relation was found in chemotherapy-naive patients with advanced NSCLC receiving paclitaxel and carboplatin, whereas paclitaxel concentrations above 0.1 μmol/L for >15 hours were related to improved overall survival (30). However, these studies did not systematically assess the effect of covariates on paclitaxel distribution and elimination. Accordingly, we intended to establish a population pharmacokinetic and covariate model of paclitaxel, given at various dose levels and infusion durations, in solid tumor patients, and to study the effect of anthropometric and biochemical variables and third-space effusions.

Materials and Methods

Patient population and blood sample analysis. Plasma concentration-time data of paclitaxel were collected during safety and pharmacokinetic studies in patients with NSCLC (30, 31), ovarian cancer (32), and various solid tumors (33), accounting for a total of 168 cancer patients and 280 treatment courses, and submitted to population pharmacokinetic analysis. Patients were recruited from two multicenter studies (30, 32) that studied paclitaxel at a dose of either 135 mg/m² (n = 2) or 175 mg/m² (n = 3) infused over 24 hours in women with recurrent epithelial ovarian cancer (32) and paclitaxel at a dose of 100 to 250 mg/m² infused over 3 hours with concurrent carboplatin (300-400 mg/m²) in patients with advanced NSCLC (n = 55; ref. 30). Additional patients with advanced ovarian cancer were entered from a study, where patients received either paclitaxel 175 or 135 mg/m² over 3 or 24 hours (29). Fifty-three patients with various solid tumors were included from a phase I study, where pharmacokinetic data were obtained from subsequent treatment cycles with i.v. paclitaxel at a dose of 175 mg/m² over 3 hours (33). Finally, 25 patients with advanced NSCLC were entered from a dose individualization study on paclitaxel (initial dose 175 mg/m² over 3 hours) and concurrent carboplatin (31). All studies were approved by the Medical Ethics Committees of the participating centers, and informed consent was obtained from all patients. Patient characteristics are outlined in Table 1. Eight of 40 patients with ovarian cancer had ascites, whereas 16 of the 84 patients with NSCLC had pleural effusions.

Paclitaxel (Taxol, Bristol Myers Squibb, Syracuse, NY) was provided as a sterile 6 mg/mL solution and dissolved in Cremophor EL/ethanol 1:1. Before administration, the solution was diluted with 500 to 1,000 mL of 0.9% sodium chloride solution to a final paclitaxel concentration between 0.3 and 1.2 mg/mL. Adapted PVC-free administration equipment was used. Standard premedication with dexamethasone (20 mg orally at 12 and 6 hours before paclitaxel administration), diphenhydramine (2 mg i.v. 30 minutes before paclitaxel administration), and a H2 receptor antagonist was administered to prevent hypersensitivity reactions.

Pharmacokinetic sampling and bioanalysis. Plasma concentration-time data from paclitaxel were obtained by pharmacokinetic sampling from one (n = 168), two (n = 111), and three treatment courses (n = 1). The samples for paclitaxel analysis were collected in heparinized tubes. In the 3-hour infusion schedules, blood samples were taken before the start of the infusion; at 1 and 2 hours after the start; at the end of the infusion; at 5, 10, 15, 30, 45, and 60 minutes; and at 1, 5, 2, 3, 4, 6, 8, 10, 12, 24, 30, and 48 hours after the end of the infusion. In the 24-hour infusion schedules, blood samples were taken before the start of the infusion; at 3, 10, and 20 hours after the start of the infusion; at the end of infusion; at 5, 15, 30, and 60 minutes; and at 2, 4, 8, 12, 24, and 30 hours after the end of infusion. Whole blood was centrifuged immediately after withdrawal during 5 minutes at 3,000 rpm, and the plasma fraction was stored at −20°C until analysis. The plasma concentrations of paclitaxel was determined by a validated isocratic high-performance liquid chromatographic method with solid-phase extraction as the sample pretreatment procedure, as has been described in detail elsewhere (34, 35). The quantitation range of the high-performance liquid chromatographic method was 10 to 10,000 ng/mL.

Basic population pharmacokinetic model. Population pharmacokinetic analysis of the concentration-time data of paclitaxel was done using the nonlinear mixed-effect modeling program (NONMEM) version V (double precision, level 1.1; ref. 36). NONMEM uses a maximum likelihood criterion to simultaneously estimate population values of fixed-effects variables (e.g., drug clearance) and values of the random-effects variables (e.g., interindividual, interoccasion, and residual variability). Log-transformed plasma drug concentrations were used together with the first-order estimation method throughout data analysis. SIs for all variables were calculated using the COVARIANCE option of NONMEM, and individual Bayesian pharmacokinetic variables were obtained with the POSTHOC option (36). The S-plus (MathSoft, Inc., Seattle, WA) based model building aid Xpose 3.0 was used for graphical processing (37). In the first step, a basic model was developed to model concentration-time data of paclitaxel. Paclitaxel concentration-time data were best described by a three-compartment model with saturable elimination from the central compartment.

Table 1. Patient characteristics (N = 168)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal range</th>
<th>Median value</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/females</td>
<td>(86/82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>56</td>
<td>331-86.2</td>
<td></td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.80</td>
<td>1.35-2.25</td>
<td></td>
</tr>
<tr>
<td>Patient weight (kg)</td>
<td>68.5</td>
<td>44-125</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase (Units/L)</td>
<td>≤40</td>
<td>13</td>
<td>3-98</td>
</tr>
<tr>
<td>Alanine aminotransferase (Units/L)</td>
<td>≤45</td>
<td>12</td>
<td>5-150</td>
</tr>
<tr>
<td>Total bilirubin (μmol/L)</td>
<td>&lt;16</td>
<td>7</td>
<td>2-24</td>
</tr>
<tr>
<td>Alkaline phosphatase (Units/L)</td>
<td>40-120</td>
<td>82</td>
<td>46-723</td>
</tr>
<tr>
<td>Gamma-glutamyl transpeptidase (Units/L)</td>
<td>≤50</td>
<td>34</td>
<td>7-4756</td>
</tr>
<tr>
<td>Lactic dehydrogenase (Units/L)</td>
<td>≤450</td>
<td>273</td>
<td>51-625</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>50-105</td>
<td>78</td>
<td>37-181</td>
</tr>
<tr>
<td>Creatinine clearance (Cockcroft-Gault) (mL/min)</td>
<td>60-140</td>
<td>78</td>
<td>37-144</td>
</tr>
</tbody>
</table>
saturable transport to the first peripheral compartment, and linear
distribution to the second peripheral compartment. The following
pharmacokinetic variables were estimated: volume of the central
(V1 in L) and second peripheral compartment (V3 in L), maximal
elimination rate (VMEL in μmol/h), Michaelis-Menten constant (KMEL,
in μmol/L), maximal transport rate to the first peripheral compartment
(VMTR in μmol/h), total plasma concentration of paclitaxel at half VMTR
(KMTR in μmol/L), and intercompartmental clearance between the
central and second peripheral compartment (Q in L/min). Model
selection was based on the minimum value of objective function of
(OFV), as calculated by NONMEM, the reliability of variable estimates
(according to the SE values of the variable estimates obtained by the
COVARIANCE option of NONMEM), and the fit of the model to the
data as approached by various graphical plots. Interindividual
variability of V1, V3, KMEL, KMTR, VMEL, VMTR, and Q and
interoccasion variability of V1, V3, VMEL, K21, and Q were estimated
using a proportional error model. For example, interindividual
and interoccasion variability of V1 was defined as follows:

\[ V_{1ij} = V_{1POP} \times (1 + \eta_{1i}^V + \epsilon_{ij}^V) \]

where \( V_{1ij} \) represents the \( V_1 \) of the \( j \)th individual, \( V_{1POP} \) is the typical
population value of \( V_1 \), \( \eta_{1i}^V \) is the interindividual random effect with
mean zero and variance \( \omega_1^2 \), and \( \epsilon_{ij}^V \) is the interoccasion random effect
with mean zero and variance \( \pi_1^2 \). Intraindividual or residual variability
was modeled as \( \log(C_i) = \log(C_{POP}) + \epsilon_i \), where \( C_i \) and \( C_{POP} \) are the
individual measures and model-predicted drug concentration of the
individual, respectively, and \( \epsilon_i \) is the residual random error with mean
zero and variance \( \sigma_1^2 \). The value of \( \sigma_2^2 \) may vary between individuals.
Therefore, the assumption of a constant \( \sigma_2^2 \) for all individuals may result
in biased variable estimates. To reduce this possible bias, two
populations with different values for \( \sigma_2^2 \) were supposed, and three
variables for the residual error model were estimated: the fractions of
subpopulations, \( \sigma_1^2 \) for population 1, and \( \sigma_2^2 \) for population 2.

**Covariate analysis.** The following covariates were tested on their
relation with all pharmacokinetic variables as mentioned above:
patient age, gender, weight, body surface area (BSA), aspartate
aminotransferase, alanine aminotransferase, performance status accord-
ing to the WHO criteria, total bilirubin, the presence of liver metastases,
third-space effusions (ascites in ovarian cancer patients and pleural
effusions in NSCLC patients, respectively), and serum albumin. Forward
selection and backward elimination were used for this purpose with OFV
as the main discriminator between different models. The difference in
the OFV of hierarchical models is equal to minus twice the log likelihood
of the data and approximates to a \( \chi^2 \) distribution with one degree of
freedom. Covariates were entered individually into the basic population
model by forward inclusion. Continuous covariates, such as patient
weight, were centered to their median values, as exemplified for \( V_1 \):

\[ V_1 = \theta_1 \times (WT - 68)^6 \]

where \( \theta_1 \) represents the \( V_1 \) value of a (median) patient with a body
weight of 68 kg, and \( \theta_2 \) is the exponential factor for patient weight
to describe the correlation with \( V_1 \). Binary covariates were coded as follows:

\[ V_1 = \theta_1 \times \theta_2^{GEN} \]

Where \( \theta_1 \) represents the \( V_1 \) value in females (GEN = 0), and \( \theta_2 \) is the
change in \( V_1 \) in males (GEN = 1). The difference in the OFV was
evaluated after the introduction of a covariate into the model (forward
inclusion), and the significance level was set at \( P < 0.01 \) that corresponds
to a decrease of OFV of >6.7. All significant covariates were included into
an intermediate multivariate model followed by a stepwise backward
elimination procedure. Covariates remained in the model when
elimination of the covariate caused an OFV increase of >7.9 (\( P < 0.005 \)). The final
covariate model was used to simulate data sets for the
comparison of covariates with paclitaxel (Cmax) and the time above the
paclitaxel threshold concentration of 0.1 μmol/L (T20.1 expressed in
hours), as the latter is known to be related to hematotoxicity (29). For
this purpose, populations of 1,000 individuals were simulated with a
specific covariate from the final model, and the distribution of Cmax and
\( T_{20.1} \) was recorded. For data simulation, all individuals were assumed to
receive paclitaxel 175 mg/m2 in a 3-hour infusion. The simulations were
separately done for male and female patients.

**Results**

**Basic population pharmacokinetic model.** Clinical data of
the patient population are outlined in Table 1. Concentration-time
data of paclitaxel were best described by a three-compartment
model with Michaelis-Menten elimination and saturable distribution
to one peripheral compartment using NONMEM subroutine ADVAN6.
Patients were divided into two subpopulations as outlined in Materials and Methods, and 15% of the
patients were allocated to subpopulation one by NONMEM,
characterized by the highest residual error. Using two subgroups
with separate residual errors was superior to adopting equal
residual errors for the whole patient group, based on OFV, SEs of
variable estimates, and graphical plots. Final population
variable estimates are outlined in Table 2. A marked interindividual
variability was found for KMTR (47.1%) and Q (36.7%). Interoccasion variability was determined for \( V_1 \), \( V_3 \), VMEL, and

<p>| Table 2. Population variables of the final paclitaxel population pharmacokinetic model |
|---------------------------------|-------|-------|</p>
<table>
<thead>
<tr>
<th>Pharmacokinetic variable</th>
<th>Estimate</th>
<th>RSE (in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_1 ) (L)</td>
<td>12.8</td>
<td>3.02</td>
</tr>
<tr>
<td>( V_3 ) (L)</td>
<td>252</td>
<td>4.68</td>
</tr>
<tr>
<td>VMEL (μmol/h)</td>
<td>37.4</td>
<td>7.49</td>
</tr>
<tr>
<td>KMEL (μmol/L)</td>
<td>0.53</td>
<td>10.4</td>
</tr>
<tr>
<td>VMTR (μmol/h)</td>
<td>169</td>
<td>5.60</td>
</tr>
<tr>
<td>KMTR (μmol/L)</td>
<td>0.83</td>
<td>11.9</td>
</tr>
<tr>
<td>( K_{21} ) (h⁻¹)</td>
<td>1.15</td>
<td>6.10</td>
</tr>
<tr>
<td>Q (L/h)</td>
<td>20.1</td>
<td>4.34</td>
</tr>
</tbody>
</table>

**Interindividual variability**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>RSE (in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_1 ) (%)</td>
<td>17.6</td>
<td>12.6</td>
</tr>
<tr>
<td>( V_3 ) (%)</td>
<td>22.5</td>
<td>15.4</td>
</tr>
<tr>
<td>VMEL (%)</td>
<td>15.9</td>
<td>7.36</td>
</tr>
<tr>
<td>VMTR (%)</td>
<td>27.7</td>
<td>12.9</td>
</tr>
<tr>
<td>KMTR (%)</td>
<td>47.1</td>
<td>24.6</td>
</tr>
<tr>
<td>Q (%)</td>
<td>36.7</td>
<td>13.2</td>
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**Interoccasion variability**

<table>
<thead>
<tr>
<th>Subpopulation</th>
<th>Estimate</th>
<th>RSE (in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (%)</td>
<td>25.9</td>
<td>17.9</td>
</tr>
<tr>
<td>2 (%)</td>
<td>34.1</td>
<td>15.7</td>
</tr>
<tr>
<td>3 (%)</td>
<td>15.2</td>
<td>6.60</td>
</tr>
<tr>
<td>4 (%)</td>
<td>18.7</td>
<td>9.21</td>
</tr>
</tbody>
</table>

**Residual variability**

<table>
<thead>
<tr>
<th>Subpopulation</th>
<th>Estimate</th>
<th>RSE (in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (%)</td>
<td>32.1</td>
<td>3.65</td>
</tr>
<tr>
<td>2 (%)</td>
<td>12.4</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Abbreviation: RSE, relative SE.

*Fraction subpopulation 1: 0.15 (RSE = 19.2%).
$K_{21}$. Inclusion of interindividual and interoccasion variability for the other pharmacokinetic variables did not improve the fit, indicating that the data do not contain sufficient information to estimate these variables. The final model suggested that nonlinear distribution of paclitaxel to the peripheral compartment is saturated at higher plasma concentrations ($K_{EL} = 0.83 \mu mol/L$ for females and $1.74 \mu mol/L$ for males) than nonlinear elimination ($K_{TR} = 0.53 \mu mol/L$). If compared with the paclitaxel plasma concentration curve of a typical patient (Fig. 1), drug elimination is saturable until ~0.5 hour after the end of paclitaxel infusion in men and until 1 hour after the end of infusion in females. By comparison, drug distribution is saturable until ~2 hours after the end of paclitaxel infusion in both male and female patients. The goodness-of-fit plots of the observed concentrations versus the (individual) predicted concentrations of the final model are depicted in Fig. 2.

**Covariate analysis.** Covariate testing by forward inclusion indicated a significant ($P < 0.01$) correlation between the following variables: patient gender with $KM_{EL}$, $VM_{EL}$, $K_{MTR}$, $VM_{TR}$, $K_{21}$ and $V_{3/4}$; patient age with $VM_{EL}$ and $Q$; BSA with $VM_{EL}$, $K_{MTR}$, $VM_{TR}$, $V_{3/4}$, and $Q$; total bilirubin with $VM_{EL}$; patient weight with $VM_{EL}$, $VM_{TR}$, and $V_{3/4}$. The presence of third-space effusions (pleural effusion in patients with NSCLC and ascites in patients with ovarian cancer) was not found to have a significant effect on paclitaxel pharmacokinetics. Stepwise backward elimination revealed significant ($P < 0.005$) correlations between covariates and pharmacokinetic variables as given in the following equations:

$$V_{3/4} \ [L] = 252 \times (\text{BSA}/1.8)^{1.17} \quad (A)$$

$$VM_{EL} \ [\mu mol/h] = 37.4 \times 1.2^\text{Gender} \times (\text{BSA}/1.8)^{0.842} \times (\text{bilirubin}/7)^{-0.167} \times (\text{age}/56)^{-0.352} \quad (B)$$

$$VM_{TR} \ [\mu mol/h] = 169 \times 1.2^\text{Gender} \times (\text{BSA}/1.8)^{0.911} \quad (C)$$

$$KM_{TR} \ [\mu mol/L] = 0.826 \times 2.11^\text{Gender} \quad (D)$$

$$K_{21} \ [h^{-1}] = 1.15 \times 0.893^\text{Gender} \quad (E)$$

$$Q \ [L/h] = 20.1 \times (\text{BSA}/1.8)^{0.724} \quad (F)$$

Patient gender is 0 for females and 1 for males. Typically, male patients had a 20% higher maximal elimination capacity ($VM_{EL}$), a 0.2 m$^2$ increase of BSA led to a 9% increase of $VM_{EL}$; a 10-year increase of patient age led to a 5% decrease of $VM_{EL}$; and a 10-µmol increase of total bilirubin led to a 14% decrease of $VM_{EL}$. According to Eq. B, maximal elimination capacity is 22% lower for the patient with the lowest BSA (1.35 m$^2$), 19% lower for the patient with the highest serum bilirubin (24 µmol/L), and 14% lower for the oldest individual studied (86 years) compared with the typical patient. $VM_{TR}$ is 20% higher for males than for females and increases with increasing BSA. $KM_{TR}$ is more than two times higher in males than in females, whereas $K_{21}$ is 11% lower in males than in females. Finally, intercompartmental clearance ($Q$) increases with increasing BSA. The inclusion of all significant covariates led to a drop in the OFV of 247.4 points compared with the model without covariates ($P < 10^{-4}$) and to a drop in individual variability for $V_{3/4}$ (from 27.0% to 22.5%), $VM_{EL}$ (from 21.1% to 15.9%), $VM_{TR}$ (from 38.1% to 27.7%), and $KM_{TR}$ (from 65.2% to 47.1%).

Data simulations for the comparison of final covariates $C_{max}$ and time above threshold concentration of 0.1 µmol/L ($T_{CO.1}$) produced the plots as outlined in Fig. 3 (for BSA) and Fig. 4 (for total bilirubin and patient age). Although paclitaxel $T_{CO.1}$ is stable over the tested BSA range in male and female patients, median values were higher in female compared with male patients. $C_{max}$ increases with BSA in male and female

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**Fig. 1.** Log-transformed concentration-time data of paclitaxel 175 mg/m$^2$ as a 3-hour infusion. Points, median; bars, SD.

**Fig. 2.** Goodness-of-fit plots of the final population pharmacokinetic model (all data log transformed). A, observed paclitaxel concentrations versus the model predictions of paclitaxel concentrations. B, observed paclitaxel concentrations versus the individual Bayesian predictions of paclitaxel concentrations.
patients and is also higher in female compared with male patients. $C_{\text{max}}$ and $T_{\text{CO.1}}$ increased over the simulated range with increasing total bilirubin concentrations and with increasing age, both in female and male patients (Fig. 4). $C_{\text{max}}$ and $T_{\text{CO.1}}$ were significantly higher in female compared with male patients ($P < 10^{-3}$ for all comparisons).

**Discussion**

The aim of this study was to quantitatively assess the effect of anthropometric, biochemical variables and third-space effusions, as outlined in Materials and Methods, on paclitaxel pharmacokinetics in patients with solid tumors, mainly NSCLC and ovarian cancer, by using a population approach. Three compartments were used to describe paclitaxel pharmacokinetic data, in accordance to what has previously been reported (2, 24, 31). Our model suggested that nonlinear distribution of paclitaxel to the peripheral compartment is saturated at higher plasma concentrations (0.83 μmol/L for females and 1.74 μmol/L for males) compared with nonlinear elimination (0.53 μmol/L). This is in accordance with one prior pharmacokinetic analysis of paclitaxel (31), but the opposite has been found in a study by Karlsson et al. (24). The interindividual variability of nonlinear drug distribution ($KM_{TR}$), however, is significant (Table 2), and the estimation of Michaelis-Menten variables might be bothersome even with rich data sets.

The presented model remains an empirical one, because it is well known that the nonlinear behavior of paclitaxel is caused by the formulation vehicle Cremophor EL and the formation of micelles in blood (3–6). These micelles act as high-affinity drug-transporting sites for paclitaxel, resulting in a decreased free paclitaxel plasma fraction and reduced uptake of paclitaxel into target tissues (3–7). A more mechanism-based population model using total, unbound plasma concentrations, and blood concentrations of paclitaxel, as well as Cremophor EL concentrations, has recently been published by Henningsson et al. (8, 25). This model supported the hypothesis that Cremophor EL is mainly responsible for the nonlinear pharmacokinetics of paclitaxel and that the unbound compound exhibits linear pharmacokinetics. Although the model implemented by Henningsson et al. is less empirical than models lacking unbound paclitaxel and Cremophor EL concentrations, it comes at the cost of additional analysis of the concentrations of unbound paclitaxel, paclitaxel in full blood, and Cremophor EL.

The exposure-toxicity relationship of paclitaxel has mostly been described with a threshold model, according to which neutropenia is related to the duration of exposure above a certain threshold concentration: ≥0.05 μmol/L (2, 21), ≥0.1 μmol/L (29), 0.07 μmol/L (26), and 0.2 μmol/L (8). Although simulations of various doses indicated a dependency of the neutropenia time course on paclitaxel exposure in animal models (38), such straightforward correlations were not found.
in humans (2, 29, 39), potentially as a consequence of the complex and nonlinear pharmacokinetic behavior of the drug. Paclitaxel drug exposure as assessed by AUC and $C_{\text{max}}$ has been analyzed in 18 ovarian cancer patients (29) and 30 patients with gynecologic tumors (2), respectively, and no correlation with drug toxicity has been shown.

Although population pharmacokinetic models of paclitaxel have been described previously (8, 24, 25), only the study by Henningsson et al. implemented NONMEM covariate testing to our knowledge (25). The latter study found a positive correlation of body size with paclitaxel elimination and a negative correlation of serum bilirubin with paclitaxel elimination (25), similar to what was found in our study in a much larger patient group. Furthermore, the presented population analysis showed paclitaxel elimination to be significantly influenced by patient gender, whereas drug elimination was 20% higher in male patients compared with female patients, and patient age, whereas drug elimination decreased by roughly 5% for each 10-year increase in age (compared with the median age of 56 years). This was supported by various simulations that showed a linear increase of the time above threshold concentration with increasing total bilirubin and increasing patient age, which suggests that these covariates are clinically relevant.

Because patient selection in clinical trials of paclitaxel required essentially normal hepatic and renal function, data on the influence of liver impairment on paclitaxel pharmacokinetics and toxicity are very limited. An early phase I and pharmacokinetic study by Venook et al. suggested prolonged exposure to paclitaxel in patients with hepatic dysfunction receiving 3-hour paclitaxel infusions (40). This observation was later confirmed by the population study of Henningsson et al. (25). Even if serum bilirubin cannot be taken as a reliable surrogate marker for liver function, it can be an indicator of liver damage and/or biliary obstruction. Data on the effect of aging on paclitaxel pharmacokinetics and toxicity are also limited. Nakamura et al. found no differences in paclitaxel pharmacokinetic variables between 92 lung cancer patients ages <70 years and 28 lung cancer patients ages >70 years in a retrospective study (41). On the contrary, and in accordance to the presented study data, Smorenburg et al. showed a significantly lower paclitaxel elimination in eight breast cancer patients ages >70 years compared with 15 solid tumor patients ages <70 years (42). The study showed a linear relationships between patient age and unbound paclitaxel elimination, with ~50% reduced drug elimination in elderly patients compared with younger patients. Lichtman et al. also reported a significant difference in AUC and total paclitaxel elimination with advancing age in 113 patients treated at a dose of 175 mg/m² paclitaxel as a 3-hour infusion (43). Two studies analyzed the effect of BSA on paclitaxel distribution and elimination by testing flat-fixed paclitaxel dosing (39, 44). Smorenburg et al. found unbound and total paclitaxel elimination to be significantly related to BSA, as they studied BSA-based dosing (175 mg/m²) versus flat-fixed dosing (300 mg) of paclitaxel in 12 solid tumor patients (44). In a second study in 32 female solid tumor patients, Miller et al. similarly found a significant correlation of BSA with paclitaxel

![Fig. 4. Simulation results with the time above the threshold concentration of 0.1 μmol/L paclitaxel plotted against total bilirubin in male (A) and female patients (B) and against patient age in male (C) and female patients (D). Straight lines represent median values, and dashed lines represent the 25th and 75th percentiles. Simulated dose was 175 mg/m² paclitaxel as a 3-hour infusion.](www.aacrjournals.org)
elimination but not with time above paclitaxel threshold concentration (39). As neither paclitaxel AUC nor BSA were correlated with nadir absolute neutrophil count, Miller et al. suggested fixed dosing of paclitaxel to be feasible in women. Although data simulations as outlined in Fig. 3 suggest BSA-based dosing to be effective in preventing excessive variability of time above paclitaxel threshold concentration, the lack of toxicity data in this study precludes speculations over the effect of BSA on paclitaxel toxicity. Besides body size, patient age, and total serum bilirubin, patient gender had a significant effect on paclitaxel elimination, an observation not previously reported to our knowledge. Most importantly, gender was shown to be an independent covariate on paclitaxel distribution and elimination (Eqs. B-E) according to NONMEM analysis. This suggests that lower body size in female patients is not the reason for decreased paclitaxel elimination but rather physiologic variables, including altered body composition and metabolic activity. The higher T1/2 values in female patients as derived from data simulations (Figs. 3 and 4) suggest female patients may be at increased risk for toxicity after three-hourly paclitaxel infusions compared with male patients, but this hypothesis can only be tested in prospective studies with toxicity assessments. Finally, third-space effusions, whereas common in the studied patient group, were not found to affect paclitaxel elimination in this analysis, probably due to the rather high distribution volume of paclitaxel.

In conclusion, this extended retrospective population analysis showed patient gender to significantly and independently affect paclitaxel distribution and elimination when given at various dosages and infusion times. Body size as assessed by BSA, total bilirubin, and patient age were confirmed to affect paclitaxel elimination. The presented pharmacokinetic model allowed quantification of the covariate effects on the elimination of paclitaxel. Future use of this model may include prospective covariate-adapted paclitaxel dosing to lower interpatient and intrapatient variability of drug exposure and toxicity.

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Quantitative Effect of Gender, Age, Liver Function, and Body Size on the Population Pharmacokinetics of Paclitaxel in Patients with Solid Tumors


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