A Physiologically Based Pharmacokinetic Model of Docetaxel Disposition: from Mouse to Man

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Abstract

Purpose: Docetaxel (Taxotere), an important chemotherapeutic agent with shown activity in a broad range of cancers, is being investigated for use in combination therapies and as an antiangiogenic agent. Docetaxel exhibits a complex pharmacologic profile with high interpatient variability. Pharmacokinetic models capable of predicting exposure under various dosing regimens would aid the rational development of clinical protocols.

Experimental Design: A pharmacokinetic study of docetaxel at 5 and 20 mg/kg was carried out in female BALB/c mice. Tissues were collected at various time points and analyzed by liquid chromatography-tandem mass spectrometry. Time course tissue distribution and pharmacokinetic data were used to build and validate a physiologically based pharmacokinetic (PBPK) model in mice. Specific and nonspecific tissue partitioning, metabolism, and elimination data were coupled with mouse physiologic variables to develop a PBPK model that describes docetaxel plasma and tissue pharmacokinetic. The PBPK model was then modified with human model variables to predict the plasma distribution of docetaxel.

Results: Resulting simulation data were compared with actual measured data obtained from our pharmacokinetic study (mouse), or from published data (human), using pharmacokinetic variables calculated using compartmental or noncompartmental analysis to assess model predictability.

Conclusions: The murine PBPK model developed can accurately predict plasma and tissue levels at the 5 and 20 mg/kg doses. The human PBPK model is capable of estimating plasma levels at 30, 36, and 100 mg/m². This will enable us to develop and test various dosing regimens (e.g., metronomic schedules and combination therapies) to achieve specific tissue and plasma concentrations to maximize therapeutic benefit while minimizing toxicity.

Docetaxel, a potent semisynthetic taxane analogue derived from the European yew tree (Taxus baccata; ref. 1), is currently used to treat breast, prostate, and non–small cell lung cancer (2–6) and is involved in more than 500 active and closed clinical trials. It exerts toxic effects by promoting microtubule assembly and inhibiting their depolymerization, causing a mitotic block (1, 7). Docetaxel is used as a single agent and in combination with other chemotherapeutics: doxorubicin, cyclophosphamide, and cisplatin (3, 4). In addition to being investigated for use in other cancer types and other combination modalities, the utility of docetaxel as an antiangiogenic agent is being studied. Docetaxel has shown antiangiogenic activity both in vitro and in vivo (8–11).

Docetaxel is currently administered as either a once-weekly (25-40 mg/m²) or a once-every-3-week (60-100 mg/m²) 1-h infusion (2, 12, 13). The response rates of the two treatment regimens are comparable; however, the toxicities seen can vary between the two (2). Neutropenia, the dose-limiting toxicity, and acute toxicities are common with the once-every-3-week regimen, whereas fatigue, asthenia, and skin and nail toxicities are experienced with the once-weekly regimen.

Although pharmacokinetics of docetaxel are linear up to 115 mg/m² and are not dependent on schedule (14), docetaxel exhibits a complex pharmacologic profile with high interpatient variability in pharmacokinetics. Docetaxel has a high volume of distribution and clearance (15–17), indicative of extensive drug distribution and protein binding. Clearance is the principal factor that affects the pharmacokinetic profile of docetaxel and has been correlated to toxicity and treatment efficacy as it relates to exposure (15–18). Serum protein binding, body surface area, and hepatic function are the major determinants of clearance (15, 16, 19). Docetaxel binds to albumin, lipoproteins, and α1-acid glycoprotein (20). Large variability in α1-acid glycoprotein levels is observed in cancer patients (21), leading to highly variable clearance rates, resulting in unpredictable toxicity and
response. It has also been shown that patients with impaired liver function have a decreased rate of docetaxel clearance and increased toxicity (15, 17). The importance of liver function on clearance is due to the extensive metabolism (70-80%) of docetaxel by cytochrome P450 enzymes, specifically CYP3A (12, 22). The CYP3A family of enzymes plays a key role in the metabolism of innumerable compounds. Various drugs can induce CYP3A or inhibit its activity. The coadministration of compounds, unavoidable in cancer therapy, can therefore affect the clearance of docetaxel.

To aid in the development of optimized clinical protocols with docetaxel and docetaxel-containing combinations, pharmacokinetic models that can predict concentrations in vivo under various dosing schema would be invaluable. Physiologically based pharmacokinetic (PBPK) models mathematically incorporate physiology, biochemistry, and chemical engineering principles to model the body as a chemical plant. The fundamental objective of PBPK modeling is to identify the principle organs or tissues involved in the disposition of the compound of interest and to correlate absorption, distribution, and elimination within and among these organs and tissues in an integrated and biologically plausible manner. Compartments in PBPK modeling, in contrast to classic compartmental modeling, represent specific organs or tissue groups. PBPK models use a large body of physiologic and physiochemical data, are capable of extrapolating between doses, routes of administration, and species, and allow for a priori prediction of plasma and tissue distribution (23).

There are currently no PBPK models for docetaxel available in the literature. We have developed a PBPK model that is capable of predicting docetaxel plasma and tissue concentrations in mice and plasma concentrations of docetaxel in humans. We conducted a pharmacokinetic study of docetaxel in mice at two different doses, 20 and 5 mg/kg, to develop the model and to validate the ability of the models for dose modification. We then adjusted physiologic and certain biochemical variables to allow for the simulation and prediction of human docetaxel pharmacokinetics. The PBPK model incorporates serum protein binding, hepatic metabolism, biliary and intestinal elimination, and urinary elimination with active secretion. Our model also uses specific and nonspecific binding of docetaxel to intracellular macromolecules in tissues.

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**Materials and Methods**

**Chemicals and reagents.** Docetaxel (Taxotere, Sanofi-Aventis) was purchased from the University of Colorado Hospital Pharmacy. Paclitaxel was purchased from Sigma Chemical Co. All other reagents were of analytic grade.

**Animals.** Eight- to 10-week-old female BALB/c mice were purchased from Simonsen Laboratories. Animals were housed in polycarbonate cages and kept on 12-h light/dark cycle. Food and water were given ad libitum. All studies were conducted in accordance with the NIH guidelines for the care and use of laboratory animals, and animals were housed in facility accredited by the American Association for Accreditation of Laboratory Animal Care. Animals were allowed to acclimate for 7 days before any handling.

**Pharmacokinetic study.** For the development of the PBPK model, a time course tissue distribution study of docetaxel was conducted in mice at doses of 20 and 5 mg/kg. Docetaxel was given by an i.v. tail vein injection as a single bolus dose. Following the 20 mg/kg dose, three mice were sacrificed at 5, 15, and 30 min and 1, 2, 4, 8, 12, and 24 h by cardiac stick exsanguinations under isoflurane anesthesia. Plasma, liver, intestine, kidney, lung, heart, muscle, and fat were resected, frozen in liquid nitrogen, and stored at -80°C before extraction and analysis. Animals to be sacrificed at 12 and 24 h after treatment were housed in metabolic cages to collect feces. Following the 5 mg/kg dose, three mice were sacrificed at 30 min and 1, 8, and 12 h by cardiac stick exsanguinations under isoflurane anesthesia. Animals to be sacrificed at 8 and 12 h after treatment were housed in metabolic cages to collect feces.

**Docetaxel liquid chromatography-tandem mass spectrometry analysis.** Analysis of docetaxel in plasma and tissues was done using a liquid chromatography-tandem mass spectrometry method based on a previously established method from our laboratory (24). Briefly, 100 μL of plasma samples were added to internal standard (500 pmol paclitaxel) extracted with 10 times volume of ethyl acetate. Samples were vortexed for 1 min and centrifuged at 10,000 × g for 10 min, and the organic phase was collected and evaporated to dryness using a rotary evaporator. Dried samples were reconstituted in 50% acetonitrile in water and analyzed using liquid chromatography and tandem mass spectrometry conditions as described previously. For all tissues analyzed (fat, gut, heart, kidney, liver, and lung), frozen tissues were homogenized at 100 mg/mL in water, and 100 μL of the tissue suspension were added to internal standard (500 pmol of paclitaxel) and extracted and prepared identically to plasma samples as described above. Standards and quality assurance/quality control samples were prepared in matrix with internal standard (plasma or tissue homogenate) and prepared identically to samples. The lower limit of quantitation for the assay under these sample preparation conditions was determined to be 2.5 pmol/mL for plasma and 0.5 nmol/g for tissues. The accuracy and precision for the assay were determined to be 94.0 ± 4.1% in plasma and ranged from 85.0% to 94.0% for accuracy and 3.2% to 5.0% for precision in tissues. Samples were stable as reconstituted in 50% acetonitrile for at least 24 h at room temperature as determined from repeated measures, and blank samples showed no background at the relevant ion transitions. Extraction efficiency from various tissues was variable (40-90%) based on analyte peak areas in standards compared with solvent standards, and postextraction addition studies suggest this is due to ion suppression rather than analyte extraction.

**PBPK model development.** We have developed a PBPK model for docetaxel that incorporates specific binding to intracellular components, liver metabolism, biliary and intestinal elimination, and urinary excretion with active secretion. This flow-limited model uses five compartments, liver metabolism, biliary and intestinal elimination, and urinary elimination with active secretion. Our model also uses specific and nonspecific binding of docetaxel to intracellular macromolecules in tissues.
concentration in the blood. Docetaxel is extensively metabolized by CYP3A isoforms primarily in the liver. In humans, hepatic transformation and subsequent elimination account for 80% of the administered dose (31). Mouse and human metabolic variables (\(K_{\text{nl}}\) and \(V_{\text{max}}\)) were estimated from previously reported studies (22, 32). The \(K_{\text{nl}}\) and \(V_{\text{max}}\) values used in our mouse and human PBPK models vary slightly from published data (Table 1). These differences can be attributed to several different factors: (a) published metabolic studies were conducted in mouse and human microsomes under in vitro conditions, (b) the strain of mouse and age used in the published metabolic study were different from the strain of mouse and age used in our study, and (c) it has also been reported that docetaxel metabolism rates in microsomes isolated from various mouse and age used in our study, and (c) the strain of mouse and age used in the published metabolic study were different from the strain of mouse and age used in our study. Docetaxel was assumed to be 90% bound to plasma proteins. It is assumed that both free and bound drug is available for uptake into the liver.

To account for binding of docetaxel to intracellular macromolecules within tissues, the concentration of docetaxel in the venous blood flow of a compartment is given by the following equation:

\[
C_{\text{VC}} = \frac{A_{\text{C}}}{(V_{\text{C}} + P_{\text{C}}) + \frac{B_{\text{C}}}{K_{\text{D}} + P_{\text{C}}}}
\]

where \(A_{\text{C}}\) is the amount of docetaxel in the compartment, \(P_{\text{C}}\) is the tissue/blood partition coefficient, \(B_{\text{C}}\) is the intracellular specific binding capacity of docetaxel within a compartment, and \(K_{\text{D}}\) is the binding affinity of docetaxel to intracellular macromolecules. The tissue/blood partitioning (Table 1) of docetaxel was measured in our laboratory as described below. The PBPK model was initially developed using only linear binding of docetaxel in the tissues; however, the addition of a nonlinear binding term at low concentrations provided more accurate model simulations compared with our measured data. This mathematical representation of linear and nonlinear binding of docetaxel to macromolecules in tissues is similar to those used to describe methotrexate (26) and 2,3,7,8-tetrachlorodibenzo-p-dioxin (27) binding and pharmacokinetics in PBPK models. The \(B_{\text{C}}\) and \(K_{\text{D}}\) for intracellular binding of docetaxel were estimated from intracellular pharmacokinetic models for paclitaxel (28) and from tissue tubulin concentration (29, 30) and binding studies (29). Kuh et al. (28) used their computational model for intracellular paclitaxel pharmacokinetics to determine the binding capacity and dissociation constant of paclitaxel to intracellular macromolecules, which were reported as 60 nmol/L and 5 nmol/L, respectively. From this, we estimated \(K_{\text{D}}\) to be 10 nmol/L (nmol/kg tissue; Table 1) for docetaxel binding in tissue because the model was developed for paclitaxel, and not docetaxel, in proliferating tumor cells (MCF-7). Because tubulin is most likely a major component of docetaxel will bind to intracellularly, our initial estimates of intracellular binding capacities were obtained from mouse and rat tissue tubulin concentration/binding capacities as measured by Wierzba et al. (29) and Sherline et al. (30), respectively. Our model uses intracellular binding capacities from 5,000 to 15,000 nmol/kg tissue (nmol/L; Table 1), which are 1.6- to 7.1-fold higher than tissue tubulin concentrations reported; however, these values are substantially lower than the intracellular binding capacity for human tumor cells reported by Kuh et al. (28). The binding capacities of tissue compartments and the dissociation constant of docetaxel to intracellular macromolecules used in the mouse PBPK model were the same as those used in the human PBPK model.

Data analysis. The predictive capability of the model was determined by calculating the median absolute performance error (MAPE%) and the median performance error (MPE%) and by comparison of calculated pharmacokinetic variables for the actual data sets versus the PBPK model simulations. The performance errors (PE) were calculated as the difference between the measured values normalized to the predicted value as shown in Eq. C (34).

\[
\text{PE} = \frac{C_{\text{measured}} - C_{\text{predicted}}}{C_{\text{predicted}}} \times 100\% 
\]

The MAPE%, which is a measure of the accuracy of the prediction, was calculated by the following equation:

\[
\text{MAPE} = \text{median}(|\text{PE}_1|, |\text{PE}_2|, \ldots, |\text{PE}_n|)
\]

where \(n\) is the total number of samples for that tissue. The MPE%, which is a measure of the bias of a prediction, was calculated by the following equation:

\[
\text{MPE} = \text{median}(\text{PE}_1, \text{PE}_2, \ldots, \text{PE}_n)
\]
The PBPK model was written and simulations were conducted in Advanced Continuous Simulation Language Tox version 11.8.4 (AEgis Technologies Group, Inc.) on a personal computer–based computer. Pharmacokinetic modeling and calculation of pharmacokinetic variables were done with WinNonlin version 4.1 (Pharsight Corp.). Student’s t test was used to determine statistical significance between two groups. Values of $P > 0.05$ were considered not statistically significant. Analyses were done with SigmaStat Statistical Software version 2.03 (SPSS, Inc.).

### Results

**Docetaxel pharmacokinetics and model simulations in mice.**

Plasma and tissue concentrations of docetaxel were measured in female BALB/c mice following a single i.v. dose of 20 or 5 mg/kg. Time points for plasma and tissue collection at the 20 mg/kg dose were selected to capture the distribution and elimination phases of drug disposition to aid the development of our PBPK model and for more accurate calculations of pharmacokinetic variables. The tissue distribution study at the 5 mg/kg dose consisted of only four time points and was used to validate the ability of our mouse PBPK model to predict plasma and tissue concentrations at a lower dose. The concentration-time profile of docetaxel in the plasma, liver, intestine, kidney, and feces (Fig. 2, *symbols*) and the resulting PBPK model simulations (Fig. 2, *solid lines*) are shown in Fig. 2A (20 mg/kg) and Fig. 2B (5 mg/kg). The resulting simulations closely approximate the actual plasma and tissue data at both dose levels.

Predictive capability of the model was determined by calculating the MAPE% and the MPE% for the plasma and
each tissue (Table 2). MAPE%, a measure of predictive accuracy, for the 20 mg/kg dose varied between 19.2% and 46.7%, and the average coefficient of variation of the actual measured data sets for plasma and tissues ranged from 17.6% to 45.3%. This indicates that the model predictions are generally within the dispersion of the data set. At the 5 mg/kg dose, the MAPE% varied from 13.5% to 197.0%, with the majority of tissues having MAPE% values of 50, and the average coefficient of variation of the actual measured data sets for plasma and tissues ranged from 7.9% to 35.3%. The MAPE% for the 5 mg/kg plasma simulation is high compared with values of the 20 mg/kg plasma simulation as well as both the 20 and 5 mg/kg tissue simulations. This is primarily due to the difference seen in the simulation versus data at the 30-min and 1-h time points. Because the 5 mg/kg tissues distribution data consist of only four time points, the discrepancies between simulation and data in just one or two time points greatly affect the MAPE%. Calculation of the MPE% showed that the simulations at both doses generally underpredicted the data (positive MPE%). Only the plasma at the 20 mg/kg dose showed an overprediction of the data set.

Comparison of pharmacokinetic variables was also done to evaluate the predictive capability of our mouse PBPK model (Table 3). The terminal half-life ($t_{1/2}$), area under the curve (AUC), and clearance were calculated for the actual and simulated data for the 20 mg/kg dose. Plasma was fit to a three-compartment model with i.v. bolus input. Pharmacokinetic variables calculated from actual plasma time course data were remarkably similar to the pharmacokinetic variables calculated from data generated by the PBPK model at the same sampling time points. Tissue pharmacokinetic variables from time course data and data generated from model simulations were calculated using noncompartmental analysis. Ratios (measured/simulated) for $t_{1/2}$ and AUC were calculated to compare the measured and the simulated values. The ratios show that both the $t_{1/2}$ and AUCs of the simulated data

Fig. 2. Plasma and tissue levels and PBPK model simulations in mice following doses of 20 mg/kg (A) and 5 mg/kg (B). Symbols, measured data; solid lines, resulting model simulations.
plasma levels were simulated at 30, 36, and 100 mg/m². The calculation. Anomalies in individual time points will have a large effect on the slope of a putative linear terminal elimination phase, discrepancy being 53% for the intestine AUC; however, the data used to calculate the intestine pharmacokinetic variables had an average coefficient of variation of 45.3%. Because data were collected at four time points for the 5 mg/kg dose, only the terminal \( t_{1/2} \) was estimated to be the terminal elimination phase. At the 5 mg/kg dose, there are larger differences between the \( t_{1/2} \) for the simulated data and the actual data than seen for the 20 mg/kg dose. The largest discrepancy between the measured and simulated data was 54% for the intestinal \( t_{1/2} \). Because \( t_{1/2} \) is calculated from the slope of a putative linear terminal elimination phase, discrepancies in individual time points will have a large effect on the calculation.

**Dose**

Table 2. Predictive performance for mouse and human PBPK model simulations

<table>
<thead>
<tr>
<th>Dose</th>
<th>Tissue/patient</th>
<th>MAPE%</th>
<th>MPE%</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg/kg</td>
<td>Plasma</td>
<td>19.2</td>
<td>-16.5</td>
</tr>
<tr>
<td></td>
<td>Liver</td>
<td>44.1</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>Intestine</td>
<td>38.4</td>
<td>38.4</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>46.7</td>
<td>37.5</td>
</tr>
<tr>
<td></td>
<td>Feces</td>
<td>27.4</td>
<td>27.4</td>
</tr>
<tr>
<td>5 mg/kg</td>
<td>Plasma</td>
<td>197.0</td>
<td>197.0</td>
</tr>
<tr>
<td></td>
<td>Liver</td>
<td>13.5</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>Intestine</td>
<td>46.3</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>50.0</td>
<td>21.5</td>
</tr>
<tr>
<td></td>
<td>Feces</td>
<td>50.8</td>
<td>4.8</td>
</tr>
<tr>
<td>30 mg/m²</td>
<td>2</td>
<td>57.6</td>
<td>57.6</td>
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<tr>
<td></td>
<td>3</td>
<td>66.2</td>
<td>66.2</td>
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<td>5</td>
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<td>34.2</td>
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<td></td>
<td>9</td>
<td>36.6</td>
<td>36.6</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>13.0</td>
<td>-13.0</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>78.2</td>
<td>78.2</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>47.1</td>
<td>47.1</td>
</tr>
<tr>
<td>36 mg/m²</td>
<td>11</td>
<td>15.4</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>18.1</td>
<td>13.9</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>27.5</td>
<td>27.5</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>18.0</td>
<td>13.9</td>
</tr>
<tr>
<td>100 mg/m²</td>
<td>Literature</td>
<td>-31.2</td>
<td>56.6</td>
</tr>
</tbody>
</table>

* MAPE% is the median absolute performance error, which is a measure of the accuracy of the prediction and is calculated by Eq. D.

* MPE% is the median performance error, which is a measure of the bias of a prediction and is calculated by Eq. E.

* Human time course data were estimated from previous published data (31). Compared well to the measured data, with the largest discrepancy being 53% for the intestine AUC; however, the data used to calculate the intestine pharmacokinetic variables had an average coefficient of variation of 45.3%. Because data were collected at four time points for the 5 mg/kg dose, only the terminal \( t_{1/2} \) was determined and compared. The \( t_{1/2} \) was calculated from the slope of the line generated from the 8- and 12-h time points, which was estimated to be the terminal elimination phase. At the 5 mg/kg dose, there are larger differences between the \( t_{1/2} \) for the simulated data and the actual data than seen for the 20 mg/kg dose. The largest discrepancy between the measured and simulated data was 54% for the intestinal \( t_{1/2} \). Because \( t_{1/2} \) is calculated from the slope of a putative linear terminal elimination phase, discrepancies in individual time points will have a large effect on the calculation.

**Discussion**

PBPK models have been developed for several clinically used chemotherapeutic agents, such as Adriamycin, 1-β-D-arabinofuranosylcytosine, cisplatin, and methotrexate (23, 26, 36). Unfortunately, the predictive capability of these models has largely been ignored, and the utility of these models has been limited to describing tissue levels in model systems. Docetaxel is an excellent compound to begin investigation of the clinical utility of these types of models for several reasons: (a) high interpatient variability in toxicity and response is observed with docetaxel treatment (12, 17, 19, 31); (b) there is a known correlation between docetaxel clearance and exposure to toxicity and response (15–18); (c) clearance is primarily affected by \( \alpha_1 \)-acid glycoprotein levels and CYP3A activity (12, 15–17, 19, 20, 31), both of which can be measured and accounted for in PBPK models; (d) PBPK models can predict clearance and exposure despite docetaxel being administered at different doses on different schedules and in combination with other compounds; and (e) PBPK models can be used to advance “model-directed” experimental design of docetaxel combination therapies and its use as an antiangiogenic agent.

We have successfully developed a first-generation PBPK model that accurately predicts plasma and tissue levels of docetaxel in mice and humans. This flow-based model, consisting of five compartments, incorporates specific and nonspecific binding of docetaxel to intracellular macromolecules in tissues and metabolic and excretory variables. The specific tissues that were previously published study (35). The simulations closely approximate the actual plasma data at both dose levels. The 100 mg/m² plasma data were estimated from a previously published article (31), and the simulation at 100 mg/m² is a reasonable approximation of these data (Fig. 3C). Predictive capability of the model was determined by calculating the MAPE% and the MPE% for the plasma for each patient or data group (Table 2). The accuracy of the predictions for the 30 and 36 mg/m² doses varied between 13.0% and 78.3%, with a median MAPE% of 47.1%, and 15.4% and 27.5%, with a median MAPE% of 18.0%, respectively. For the 100 mg/m² dose, the accuracy of the prediction was 56.6%. Calculation of the MPE% showed that the low-dose simulations generally underpredicted the data (positive MPE%), with only 2 of 11 total patients having negative values, and the high-dose simulation overpredicted the data.

Pharmacokinetic variables were calculated for individual patient data sets and the corresponding simulation. A three-compartment model was used for the low docetaxel groups. The \( x_{1/2}, \beta, \gamma \), AUC, and clearance values are reported in Table 3. Student’s \( t \) test was done to compare the pharmacokinetic variables for the actual data versus the simulated data. This revealed no statistically significant differences (\( P > 0.05 \)) between pharmacokinetic variables calculated from actual data sets and from data generated by the model at both the 30 and 36 mg/m² doses. A noncompartmental model was used for the 100 mg/m² dose because data were estimated from literature and data were only available for up to 13 or 24 h. The \( x_{1/2}, \gamma \), AUC, and clearance values are reported in Table 3. The data show that the pharmacokinetics of 100 mg/m² simulations closely approximate the pharmacokinetics of the measured data.
selected for individual compartments were the kidney, liver, and intestine, whereas the remaining tissues were combined into slowly or richly perfused compartments. The kidney was selected because it is responsible for urinary elimination of docetaxel via glomerular filtration and, as our model suggests, active secretion. The liver and intestine are responsible for fecal elimination, and metabolism primarily takes place in the liver.

The utility of PBPK modeling lies in its ability to describe concentration-time profiles for individual organs. We first developed the PBPK model in mice because we were able to obtain docetaxel tissue concentrations, which for obvious reasons is not feasible in humans. This allowed us to estimate certain model variables and to begin to investigate how various model variables affected tissue concentrations by fitting the model to data. This is critical in PBPK model development because alteration in model variables can sometimes have no effect on the plasma pharmacokinetics or time course but can greatly affect specific tissue concentrations and pharmacokinetics. The pharmacokinetic studies we conducted in mice were used to generate data for this reason. The 20 mg/kg dose was chosen because 20 mg/kg every 4 days for three doses repeated every 21 days is the maximum tolerable dose in mice. A lower dose of 5 mg/kg was chosen because our laboratory is interested in investigating the effects of maximum tolerable dose dosing versus protracted schedules.

The next logical step is to modify and validate the model to include a tumor compartment. This will be critical for docetaxel because (a) tissue tubulin concentration affects docetaxel uptake and it has been shown that tumor cells can alter tubulin isotype to reduce docetaxel binding and therefore cytotoxicity (37, 38); (b) another mechanism of tumor resistance is through expression of P-glycoprotein, for which docetaxel is a substrate (39); and (c) response can be correlated to tumor exposure to docetaxel, so an understanding of tumor exposure and how it relates to measurable plasma pharmacokinetics is critical.

Docetaxel is an important chemotherapeutic agent and a model of disposition that includes terms to describe process-specific metabolism and excretion has great potential for predicting the

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**Table 3. Pharmacokinetic variables from mouse and human pharmacokinetic studies and from PBPK model simulations**

<table>
<thead>
<tr>
<th>Mouse</th>
<th>Tissue</th>
<th>$\lambda$-$t_{1/2}$ (a)</th>
<th>$AUC_{0-24}^*$ (h $\mu$mol/L)</th>
<th>$CL$ (L/h)</th>
<th>$t_{1/2}$ ratio</th>
<th>$AUC_{0-24}$ ratio $^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg/kg</td>
<td>Plasma</td>
<td>Actual</td>
<td>8.6</td>
<td>19.3</td>
<td>0.024</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Simulated</td>
<td>7.3</td>
<td>19.9</td>
<td>0.023</td>
<td>1.18</td>
</tr>
<tr>
<td></td>
<td>Liver</td>
<td>Actual</td>
<td>6.1</td>
<td>94.0</td>
<td>0.0048</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simulated</td>
<td>6.2</td>
<td>81.2</td>
<td>0.0055</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>Intestine</td>
<td>Actual</td>
<td>5.9</td>
<td>158.8</td>
<td>0.0028</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simulated</td>
<td>7.1</td>
<td>103.5</td>
<td>0.0042</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>Actual</td>
<td>5.0</td>
<td>145.7</td>
<td>0.0031</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simulated</td>
<td>9.3</td>
<td>134.4</td>
<td>0.0030</td>
<td>0.54</td>
</tr>
<tr>
<td>5 mg/kg</td>
<td>Plasma</td>
<td>Actual</td>
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<td></td>
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<td>Simulated</td>
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<td>0.61</td>
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<td></td>
<td>Liver</td>
<td>Actual</td>
<td>4.7</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Simulated</td>
<td>6.6</td>
<td></td>
<td></td>
<td>0.71</td>
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<tr>
<td></td>
<td>Intestine</td>
<td>Actual</td>
<td>3.2</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Simulated</td>
<td>6.9</td>
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<td></td>
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<td>Actual</td>
<td>5.2</td>
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<tr>
<td></td>
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<td>Simulated</td>
<td>9.2</td>
<td></td>
<td></td>
<td>0.57</td>
</tr>
<tr>
<td>Human</td>
<td>Tissue</td>
<td>$\alpha$-$t_{1/2}$ (min)</td>
<td>$\beta$-$t_{1/2}$ (h)</td>
<td>$\gamma$-$t_{1/2}$ (h)</td>
<td>$\lambda$-$t_{1/2}$ (h)</td>
<td>$AUC_{0-24}$ (h $\mu$mol/L)</td>
</tr>
<tr>
<td>30 mg/m$^2$</td>
<td>Plasma</td>
<td>Actual$^*$</td>
<td>7.4 ± 2.9</td>
<td>1.4 ± 0.3</td>
<td>27.5 ± 5.5</td>
<td>1.02 ± 0.39</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simulated$^*$</td>
<td>7.2 ± 3.6</td>
<td>1.1 ± 0.5</td>
<td>21.0 ± 10.9</td>
<td>0.96 ± 0.56</td>
</tr>
<tr>
<td>36 mg/m$^2$</td>
<td>Plasma</td>
<td>Actual$^*$</td>
<td>7.4 ± 2.2</td>
<td>2.1 ± 1.4</td>
<td>21.9 ± 7.7</td>
<td>0.95 ± 0.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simulated$^*$</td>
<td>9.3 ± 6.5</td>
<td>1.1 ± 0.4</td>
<td>17.3 ± 0.5</td>
<td>0.66 ± 0.03</td>
</tr>
<tr>
<td>100 mg/m$^2$</td>
<td>Plasma</td>
<td>Actual$^*$</td>
<td>8.2 ± 5.0</td>
<td>2.94 ± 1.62</td>
<td>77.2 ± 73.3</td>
<td>3.15</td>
</tr>
</tbody>
</table>

NOTE: Pharmacokinetic variables were calculated using noncompartmental analysis. Plasma pharmacokinetic variables for mouse 20 mg/kg and human 30 and 36 mg/m$^2$ doses were calculated using a three-compartment model. Data represent the mean ± SD from six or three patient data sets for 30 and 36 mg/m$^2$ doses, respectively.

Abbreviation: CL, clearance.

$^*$ $\lambda$-$t_{1/2}$ is the estimated terminal $t_{1/2}$ for drug elimination from plasma or tissue as estimated from linear regression of the terminal elimination phase.

$^*$ $AUC_{0-24}$ represents the AUC calculated from time 0 to 24 h.

$^*$ Ratio of the value generated for that variable from the measured versus the simulated data sets.

$^*$ Human time course data were provided by Drs. Gail Eckhart and Cindy O’Bryant (University of Colorado Health Sciences Center, Denver, CO) and have been previously published (35).

$^*$ Simulated time course data were generated using our PBPK model with actual patient weight, dose (30 or 36 mg/m$^2$ multiplied by body surface area), and infusion time set in the model.

$^*$ Pharmacokinetic variables were calculated using noncompartmental analysis.

$^*$ Human time course data were estimated from previously published data (35).

$^*$ Simulated time course data were generated using our PBPK model with an estimated patient weight of 70 kg, dose of 100 mg/m$^2$, and body surface area of 1.75m$^2$. 
effects of other xenobiotics on docetaxel pharmacokinetics. PBPK models can be coupled to Monte Carlo simulation, which can then account for variability across model variables, such as induction of CYP3A activity or reduction of CYP3A activity due to impaired liver function or competitive inhibition by a coadministered drug. We have previously shown the ability of a PBPK model coupled to Monte Carlo simulation to predict the interaction of paclitaxel on doxorubicin pharmacokinetics (40). This study showed that paclitaxel did not affect plasma pharmacokinetics of doxorubicin but did affect tissue pharmacokinetics. The establishment and use of a PBPK model capable of predicting docetaxel exposure would be beneficial in the rational design of clinical dosing schedules.

**Acknowledgments**

We thank Dr. Cindy O'Bryant for providing us with human patient information, Dr. Joseph Zirrolli for his help with the docetaxel liquid chromatography-mass spectrometry analysis, Dr. Patrick J. Kerzic for his assistance during the animal studies, and Andrea Merz for her assistance with the pharmacokinetic studies and for her help with the manuscript.

Fig. 3. Plasma levels and PBPK model simulations in humans following doses of 30 mg/m² (A), 36 mg/m² (B), and 100 mg/m² (C). Symbols, measured data for the 30 and 36 mg/m² doses; solid lines, resulting model simulations. For the 100 mg/m² dose, symbols represent data estimated from a previously published manuscript (31).
References


A Physiologically Based Pharmacokinetic Model of Docetaxel Disposition: from Mouse to Man

Erica L. Bradshaw-Pierce, S. Gail Eckhardt and Daniel L. Gustafson


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