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The Journal of Clinical Pharmacology
2020, 60(3) 340–350

DOI: 10.1002/jcph.1532

A Population Pharmacokinetic Model of Oral Docetaxel Coadministered With Ritonavir to Support Early Clinical Development

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Abstract

Oral administration of docetaxel is an attractive alternative for conventional intravenous (IV) administration. The low bioavailability of docetaxel, however, hinders the application of oral docetaxel in the clinic. The aim of the current study was to develop a population pharmacokinetic (PK) model for docetaxel and ritonavir based on the phase 1 studies and to support drug development of this combination treatment. PK data were collected from 191 patients who received IV docetaxel and different oral docetaxel formulations (drinking solution, ModraDoc001 capsule, and ModraDoc006 tablet) coadministered with ritonavir. A PK model was first developed for ritonavir. Subsequently, a semiphysiological PK model was developed for docetaxel, which incorporated the inhibition of docetaxel metabolism by ritonavir. The uninhibited intrinsic clearance of docetaxel was estimated based on data on IV docetaxel as 1980 L/h (relative standard error, 11%). Ritonavir coadministration extensively inhibited the hepatic metabolism of docetaxel to 9.3%, which resulted in up to 12-fold higher docetaxel plasma concentrations compared to oral docetaxel coadministered without ritonavir. In conclusion, a semiphysiological PK model for docetaxel and ritonavir was successfully developed. Coadministration of ritonavir resulted in increased plasma concentrations of docetaxel after administration of the oral formulations of ModraDoc. Furthermore, the oral ModraDoc formulations showed lower variability in plasma concentrations between and within patients compared to the drinking solution. Comparable exposure could be reached with the oral ModraDoc formulations compared to IV administration.

Keywords

docetaxel, ModraDoc, oral, population PK, ritonavir

Docetaxel is a widely used anticancer agent acting by inhibition of mitosis. It is approved for the treatment of breast cancer, prostate cancer, non–small cell lung cancer, head and neck cancer, and gastric cancer. Docetaxel is most commonly administered as a 3-weekly 1-hour infusion, although it has been shown that once-weekly administration is associated with comparable efficacy, while incidence of neutropenia is reduced.[1,2] A weekly schedule is infrequently used, most likely due to inconvenience for the patient associated with weekly clinic visits. An oral formulation of docetaxel would allow patients to receive docetaxel at home, thereby reducing the burden for patients and costs. In addition, oral administration would avoid the regularly observed infusion reactions, induced by the formulation additives polysorbate 80 and ethanol.[3]

After oral administration of docetaxel, low bioavailability and wide inter- and intrapatient variability in systemic exposure has been observed. In the gut and liver, docetaxel is excreted by the P-glycoprotein (ABCB1) efflux transporter and metabolized by cytochrome P450 3A4 (CYP3A4) into inactive metabolites.[4] Previously, we have shown in a proof-of-concept study that coadministration of the CYP3A inhibitor ritonavir results in a strong boost of the systemic exposure of oral docetaxel.[5] In this study, the intravenous (IV) docetaxel formulation was ingested orally as a drinking solution. Further, a solid dispersion capsule formulation, ModraDoc001, was developed and clinically evaluated with different dose levels of ritonavir.[6] Subsequently, a further improved

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Submitted for publication 15 August 2019; accepted 20 September 2019.

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Table 1. Overview of Included Clinical Studies

	Study 1 (5)	Study 2 (6, 11, 12)	Study 3a (14)	Study 3b (7)
Number of patients				
Total	37	100	48	6
Intravenous administration docetaxel	32	19	...	...
Oral docetaxel formulation of ModraDoc001 capsule	...	72	17	6
Oral docetaxel formulation of ModraDoc006 tablet	...	18	28	...
Oral docetaxel formulation of drinking solution	25	13	...	...
Docetaxel				
Oral dose levels (mg/day)	10, 100	20, 30, 40, 60, 80	40, 50, 60, 80	40
Intravenous dose levels	100 mg/m^2	20 mg	...	...
Dosing time (h)	t = 0, t = 1	t = 0	t = 0, 7	t = 0
Formulation	Intravenous Drinking solution	Intravenous Drinking solution ModraDoc001 ModraDoc006	ModraDoc001 ModraDoc006	ModraDoc001
Pharmacokinetic data	Yes	Yes	Yes	Yes
Ritonavir				
Dose (mg/day)	0, 100	0, 100, 200	200	100, 200
Dosing time (h)	t = 0	t = 0	t = 0, 7	t = 0
Ritonavir formulation	Capsules	Capsules Tablets	Tablets	Tablets
Pharmacokinetic data	No	Yes	Yes	Yes

solid dispersion tablet formulation, ModraDoc006, was developed and evaluated similarly.[7]

Modeling and simulation can be used to support clinical development.[8] Previously, we described how modelling and simulation was used to bridge oral docetaxel exposure of the preclinical and the clinical setting,[9] and to quantitatively study the effect of inhibition of CYP3A4 on docetaxel pharmacokinetics (PK) after oral administration of the IV formulation (drinking solution).[10] These models, however, did not include the PK of the dedicated oral formulations (ModraDoc001 and ModraDoc006) that were developed thereafter, and also did not include PK data of ritonavir, which was not yet available at that time. However, an integrated docetaxel-ritonavir model is needed to compare different dosing regimens of docetaxel and different oral docetaxel formulations to support decision making in the clinical development.

The objectives of the current analysis were to update a previously developed, integrated, semiphysiological PK model for docetaxel[10] with data from the novel formulations and by including ritonavir PK data. Subsequently, the model was used to support clinical development of the combination of oral docetaxel and ritonavir.

Methods

Clinical Studies

All available PK data from clinical studies evaluating the different formulations of docetaxel including the IV formulation administered intravenously and orally, and the oral solid dispersion formulations ModraDoc001 and ModraDoc006, were included. An overview of the different clinical studies is provided in Table 1. In the following sections, the studies are further summarized.

Study 1. Study 1 was a proof-of-concept study evaluating ritonavir as a booster of oral docetaxel. Docetaxel was administered intravenously at a dose of 100 mg/m^2 or as a drinking solution at a single dose of 10 or 100 mg in combination with ritonavir soft gel capsules (Norvir; Abbott Laboratories, Abbott Park, Illinois) at a dose of 100 mg. For a detailed description of this study, see Oostendorp et al.[5]

Study 2. Study 2 was a phase 1 dose-escalation study of orally administered docetaxel in combination with ritonavir in a weekly once-daily schedule. Patients received the approved IV formulation and/or 3 different oral docetaxel formulations: the orally administered IV formulation (drinking solution), the ModraDoc001 capsule formulation, and the ModraDoc006 tablet formulation. Initially, the soft gel capsule formulation (Norvir) of ritonavir was used. A switch to a ritonavir tablet formulation was made after the manufacturer switched to a tablet formulation during execution of the study. Docetaxel was administered in doses of 20 to 80 mg. Ritonavir was administered as a 100-mg or 200-mg dose. For a more detailed description of these studies, see Moes et al,[6] Koolen et al,[11] Marchetti et al,[12] and de Weger et al.[13]

Study 3a. Study 3a was a phase 1 dose-escalation study in which a weekly twice-daily dose of docetaxel

formulated as ModraDoc001 capsules or ModraDoc006 tablets, together with ritonavir, was given at t = 0 and t = 7 hours. The total daily dose of docetaxel was between 40 and 80 mg and ritonavir 200 mg. For a detailed description of Study 3a, see de Weger et al.[14]

Study 3b. Study 3b was a crossover study aiming at comparing the exposure of different ModraDoc formulations simultaneously administered with ritonavir. From this study only the development of ModraDoc001 was carried forward, so only PK data from this formulation were included in the current analysis. Docetaxel was administered at 40 mg. Ritonavir was administered at 100 or 200 mg. For a detailed description of Study 3b, see Moes et al.[7]

Model Development

Structural Model Development. The PK model for the coadministration of ritonavir and oral docetaxel was sequentially developed.[15] In the first step, a PK model for ritonavir was developed. Transit compartment models, first-order absorption, and several complex absorption models were tested to describe the ritonavir absorption. Potential autoinhibition of metabolism of previous dosing was implemented by introducing an empirical parameter describing the relative bioavailability of the second dose versus the first dose ($F_{2nd/1st,\ rtv}$).[16] More mechanistic approaches were explored, but insufficient data were available to support these models. Similarly, the effect of the formulation switch from capsule to tablet was accounted for by introducing a parameter describing the relative bioavailability of the tablet formulation versus the capsule formulation ($F_{tablet/capsule}$).

In the second step, a model for oral docetaxel, including the effects of ritonavir on oral docetaxel PK, was developed. Individual parameter estimates of ritonavir were generated from the ritonavir PK model and used as an input for docetaxel model development.[15] Previously, we established a simplified semimechanistic PK model for docetaxel solely based on PK data of the IV formulation and drinking solution.[10] We updated this model and used the well-stirred assumptions for hepatic clearance[17] as the starting point for further development. After fixing the PK for IV docetaxel, a semiphysiological approach was explored for the oral formulations, which included separate compartments for the gut, liver, and central and peripheral compartments. In this model, the inhibitory effect of ritonavir on gut wall metabolism and hepatic metabolism of docetaxel were studied, respectively.

Statistical Model Development. Inclusion of between-subject variability (BSV) and within-subject variability (WSV) was guided by the change of objective function value (OFV, minus twice the log likelihood), standard errors, and clinical relevance. Two types of WSV were identified. Within-day variability was considered for patients who were dosed twice-daily, and between-day variability was defined as variability between days of administration. BSV and WSV were modeled according to equation 1.

$$P_i = P \cdot \exp(\eta_{i,BSV} + \eta_{i,WSV}) \quad (1)$$

where P_i represents the individual parameter estimate for individual i, P represents the typical population parameter estimate, and η_i either BSV or WSV effect distributed following $N\ (0,\ \omega^2)$. Residual errors were described by proportional error models for both ritonavir and docetaxel, respectively (equation 2).

$$C_{obs},\ ij = C_{pred},\ ij \cdot (1 + \varepsilon_{p,ij}) \quad (2)$$

where $C_{obs,ij}$ or $C_{pred,ij}$ represents, for the ith subject and the jth measurement, the observation or prediction. Proportional error $\epsilon_{p,ij}$ was assumed distributed following $N\ (0,\ \sigma^2)$.

Comparison of the Characteristics of Different Docetaxel Oral Formulations. Parameters of the PK model on absorption processes and bioavailability for different docetaxel formulations were separately estimated and compared. Furthermore, it was investigated whether there were differences in the BSV and WSV of different formulations and in the PK between once-daily and twice-daily administrations. In addition, potential saturable absorption was explored for oral docetaxel.

Model Evaluation

Model evaluation was performed throughout model building by consideration of parameter precision, plausibility of parameter estimates, goodness-of-fit diagnostics, inspection of the correlation matrix, drop of OFV with significance level of $P < .01$ (degree of freedom [df] = 1, dOFV > 6.63; df = 2, dOFV > 9.21) for hierarchical models, and also visual predictive checks (n = 1000).

Simulations

Simulation studies were performed for the ModraDoc006 tablet formulation and ritonavir tablet combination, as these formulations were selected for further clinical development. In all simulations, a dose of 100-mg ritonavir was administered simultaneously with docetaxel.

The PK profiles of IV docetaxel in approved dosing schedules were compared to the different oral formulations. The docetaxel plasma concentration levels were simulated for oral docetaxel coadministered with ritonavir under the following dosing regimens of docetaxel: 40 mg, 60 mg, and 80 mg once daily; 20 mg twice daily

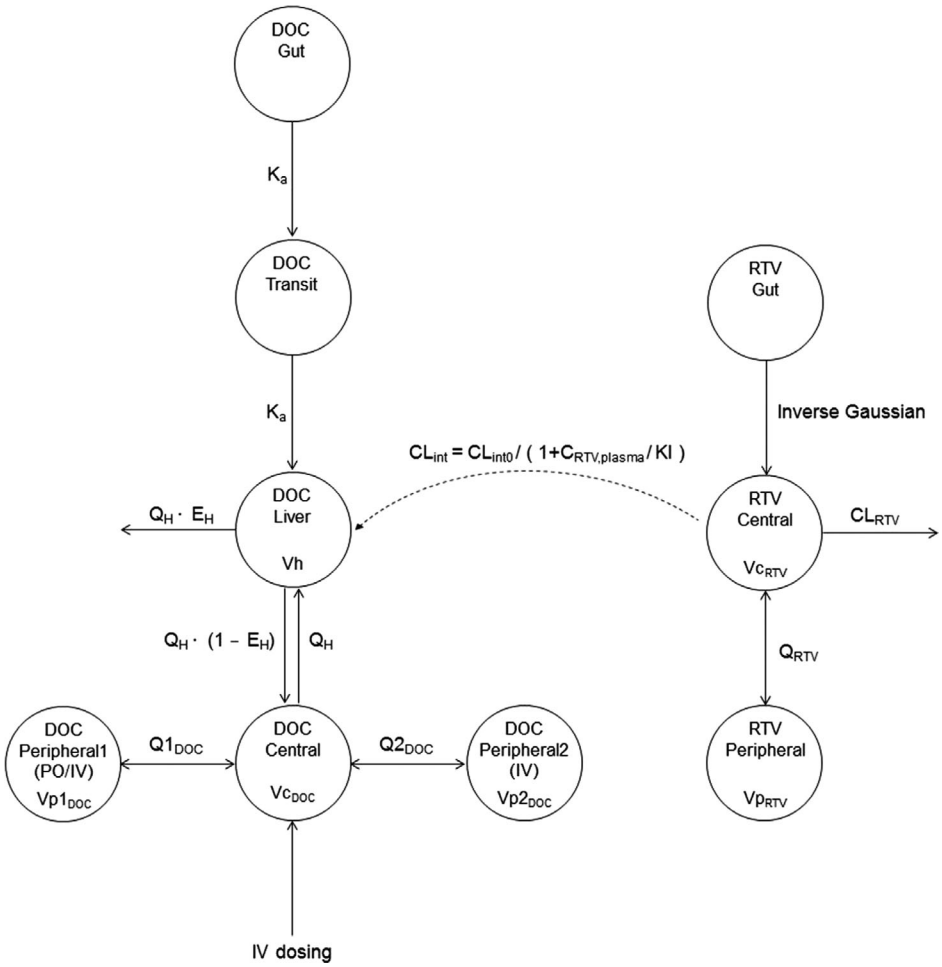

Figure 1. Schematic representation of the integrated pharmacokinetic model for docetaxel and ritonavir. CL, clearance; CL_{int}, intrinsic clearance of docetaxel; CL_{int0}, uninhibited intrinsic clearance of docetaxel; $C_{RTV,plasma}$, ritonavir plasma concentration; DOC, docetaxel; E_H, hepatic extraction ratio; K_a, first-order absorption rate constant; IV, intravenous; KI, inhibition constant of ritonavir on docetaxel metabolism; PO, oral; Q, intercompartment distribution; Q_H, hepatic blood flow; RTV, ritonavir; Vc, central volume of distribution; Vh, hepatic volume of distribution; Vp, peripheral volume of distribution. Intravenous docetaxel distributes to docetaxel peripheral compartments 1 and 2; oral docetaxel distributes only to docetaxel peripheral compartment 1.

(20/20 mg), 30 mg followed by 20 mg (30/20 mg), and 30 mg twice daily (30/30 mg). For IV docetaxel, simulations were performed based on the 3 dosing regimens used in clinical practice: 3-weekly 75 mg/m^2 with 1-hour infusion; 3-weekly 100 mg/m^2 with 1-hour infusion; and weekly 35 mg/m^2 with 0.5-hour infusion (assumed body surface area of 1.8 m^2). The area under the concentration-time curve for consecutive 96 hours after administration (AUC_{96hrs}) was used to compare once-daily and twice-daily doses. Meanwhile, the effect of the inhibition of ritonavir on the metabolism of docetaxel was assessed by comparing the docetaxel hepatic intrinsic clearance with and without coadministration of ritonavir. Because the dosing interval for IV docetaxel is usually 3 weeks, the area under the concentration-time curve for consecutive 3 weeks after administration (AUC_{3wks}) was used to compare the PK profiles of IV and oral docetaxel at different dose regimens.

Software

All model estimation was performed using NONMEM (version 7.3.0; ICON Development Solutions, Manchester, UK)[18] together with a gfortran compiler, using first-order conditional estimation with interaction. Piraña (Certara, Princeton, New Jersey) was used as graphical interface,[19] and R (version 3.0.3) was used for preprocessing of the data, plotting, and model simulation.[20] In addition, the NONMEM toolkit PsN,[21] and the R-packages Xpose[22] and deSolve[23] were used.

Results

Model Development

The schematic structure of the final model is presented in Figure 1. The parameter estimates of the final model for ritonavir and docetaxel are listed in Table 2 and Table 3, respectively.

Table 2. Parameter Estimates of Ritonavir in the Final Pharmacokinetic Model

Parameters	Units	Estimate	RSE (%)	Shrinkage (%)
Population parameter–ritonavir				
MAT	h	8.45	5	...
CV	%	123	3	...
CL_{RTV}	L/h	7.72	9	...
Vc_{RTV}	L	23	15	...
Q_{RTV}	L/h	3.99	15	...
Vp_{RTV}	L	17.9	12	...
$F_{2nd/1st,rtv}$	...	2.25	7	...
$F_{tablet/capsule}$	...	1.06	12	...
Between-subject variability				
CV	CV%	12.8	22	45
CL_{RTV}	CV%	46.7	13	25
Vc_{RTV}	CV%	93.5	10	19
F	CV%	52.2	14	23
$F_{2nd/1st}$	CV%	33.5	18	51
$F_{tablet/capsule}$	CV%	30	58	67
Within-subject variability				
MAT	CV%	32.1	7	...
CV	CV%	22.2	9	...
Residual unexplained variability				
Proportional residual error	CV%	35.2	2	12

CL_{RTV}, clearance; CV, variability of absorption time; CV%, coefficient of variation; F, relative bioavailability; $F_{2nd/1st,rtv}$, relative bioavailability of the second dose to the first dose; $F_{tablet/capsule}$, relative bioavailability of tablet to capsule; MAT, mean absorption time; Q_{RTV}, intercompartment clearance; RSE, relative standard error; RTV, ritonavir; Vc_{RTV}, volume of distribution of central compartment; Vp_{RTV}, volume of distribution of peripheral compartment.

Ritonavir PK Model. A 2-compartment model with a first-order elimination process best fitted the ritonavir plasma concentrations. The absorption of ritonavir was best described by the inverse Gaussian density-input function (equation 3).

$$N_{in} = A_D \left[\frac{MAT}{2\pi CV^2 t^3}\right]^{1/2} \cdot \exp\left(-\frac{(t-MAT)^2}{2CV^2 MAT\, t}\right) \quad (3)$$

where N_{in} is the incoming transport flux, A_D is the administered dose, MAT is the mean absorption time, and CV^2 the term expressing the variation in absorption time.[24] The second administration of ritonavir (approximately 7 hours after the first administration) showed 2.3-fold (relative standard error [RSE], 7%) higher relative bioavailability than that of the first administration. Switching of formulation from capsule to tablet resulted in a small increment in relative bioavailability of 6% (RSE, 12%).

Docetaxel PK Model. The final PK model of oral docetaxel was a multicompartmental model in which docetaxel after administration passed through 1 transit compartment to the liver compartment. Subsequently, docetaxel is metabolized by CYP3A4 in the liver or distributes between central and liver compartments. Finally, docetaxel can further distribute between central and peripheral compartment(s). Two peripheral compartments best described the PK of the docetaxel IV formulation, while 1 peripheral compartment was best suited for oral formulations (Figure 1).

The influence of each oral formulation of docetaxel without ritonavir coadministration on the overall gut bioavailability (F_G) was separately estimated as $F_{formulation}$. The inhibitory effect of ritonavir on gut wall metabolism resulting in an increased F_G was characterized by an empirical effect ($F_{ritonavir}$) defined as the ratio of bioavailability in combination with ritonavir vs without coadministration of ritonavir. A time-dependent accumulation of this inhibitory effect was considered on F_G of the second dose relative to the first dose ($F_{2nd/1st,\,doc}$). Therefore, the F_G of docetaxel was defined according to equation 4:

$$F_G = F_{formulation} \cdot F_{ritonavir} \cdot F_{2nd/1st,doc} \quad (4)$$

Docetaxel hepatic intrinsic clearance (CL_{int}) was determined as a function of the uninhibited intrinsic clearance (CL_{int0}) and the ritonavir plasma concentration ($C_{RTV,plasma}$) (equation 5) in which KI is the inhibition constant of CYP3A4 by ritonavir. Based on well-stirred assumptions, docetaxel extraction ratio (E_H) and hepatic bioavailability (F_H) were defined as follows (equations 6 and 7):

$$CL_{int}(t) = CL_{int\,0}(t)/(1 + C_{RTV,\,plasma}(t)/KI) \quad (5)$$

$$E_H(t) = \frac{CL_{int}(t) \cdot fu}{Q_H + CL_{int}(t) \cdot fu} \quad (6)$$

$$F_H(t) = 1 - E_H(t) \quad (7)$$

Here, hepatic blood flow Q_H was fixed at a value of 80 L/h^{-1}.[25] As only total concentrations of docetaxel (eg, free and protein bound) were available, we assumed literature-reported estimates for the fractions of unbound docetaxel (fu) of 4.6%.[26] The volume of the liver compartment (Vh) was assumed as 1 L, which is close to the empirically determined value.[27]

Table 3 shows the parameter estimates of the model for IV and oral docetaxel. Based on the PK data of IV docetaxel, the CL_{int0} was estimated at 1980 L/h (RSE, 11%). For oral docetaxel formulations, the second coadministration in twice-daily dosing showed an increase of 12% (RSE, 7%) in F_G compared to the first. Coadministration of ritonavir resulted in 3.7-fold (RSE, 28%) higher F_G than oral docetaxel without ritonavir. The KI of ritonavir was estimated at 210 ng/mL (RSE, 40%).

Table 3. Parameter Estimates of Docetaxel in the Final Pharmacokinetic Model

Formulations of Docetaxel		Oral Formulations			Intravenous Formulation		
Parameters	Units	Estimate	RSE (%)	Shrinkage (%)	Estimate	RSE (%)	Shrinkage (%)
Population parameter–docetaxel							
First-order k_a–ModraDoc001 capsule	h^{-1}	1.4	7	...	...	...	...
First-order k_a–ModraDoc006 tablet	h^{-1}	0.95	10	...	...	...	...
First-order k_a–drinking solution	h^{-1}	1.84	17	...	...	...	...
CL_{int0}	L/h	1980 FIX[a]	...	...	1980	11	...
KI	ng/mL	210	40	...	210	20	...
Vc_{DOC}	L	119	12	...	5.38	10	...
$Q1_{DOC}$	L/h	29.8	6	...	15.4	5	...
$Vp1_{DOC}$	L	582	6	...	400	5	...
$Q2_{DOC}$	L/h	...	...	...	5.56	6	...
$Vp2_{DOC}$	L	...	...	...	7.68	4	...
$F_{ritonavir}$	...	3.66	28	...	...	...	...
$F_{2nd/1st,\ doc}$	...	1.12	7	...	...	...	...
$F_{formulation,ModraDoc001}$	...	0.18	23	...	...	...	...
$F_{formulation,ModraDoc006}$	...	0.22	24	...	...	...	...
$F_{formulation,drinking\ solution}$	...	0.27	25	...	...	...	...
Between-subject variability							
k_a–ModraDoc001 & ModraDoc006	CV%	37.3	16	43	...	...	...
k_a–drinking solution	CV%	81.7	18	63	...	...	...
CL_{int0}	CV%	38.7	16	29	60	10	3
Vc_{DOC}	CV%	46.2	14	23	82.2	6	7
F_G–ModraDoc001 & ModraDoc006	CV%	35.8	14	34	...	...	...
F_G–drinking solution	CV%	74.2	15	59	...	...	...
Within-subject variability							
Between-day variability on k_a–ModraDoc001 & ModraDoc006	CV%	43.1	12	...	...	...	...
Between-day variability on k_a–drinking solution	CV%	39.5	21	...	...	...	...
Within-day variability on k_a–ModraDoc001 & ModraDoc006	CV%	50.9	13	...	...	...	...
Between-day variability on F_G–ModraDoc001 & ModraDoc006	CV%	29.1	8	...	...	...	...
Between-day variability on F_G–drinking solution	CV%	39.5	21	...	...	...	...
Within-day variability on F_G–ModraDoc001 & ModraDoc006	CV%	25.2	21	...	...	...	...
Residual unexplained variability							
Proportional residual error	CV%	37.4	4	8	26.5	6	7

CL_{int0}, uninhibited intrinsic clearance; CV%, coefficient of variation; DOC, docetaxel; $F_{2nd/1st,\ doc}$, gut bioavailability of the second dose relative to the first dose; $F_{formulation,drinking\ solution}$, gut bioavailability of drinking solution without ritonavir coadministration; $F_{formulation,ModraDoc001}$, gut bioavailability of ModraDoc001 without ritonavir coadministration; $F_{formulation,ModraDoc006}$, gut bioavailability of ModraDoc006 without ritonavir coadministration; F_G, gut bioavailability; $F_{ritonavir}$, gut bioavailability in combination with ritonavir relative to without; k_a, absorption rate constant; KI, inhibition constant; $Q1_{DOC}$, intercompartment clearance 1; $Q2_{DOC}$, intercompartment clearance 2; RSE, relative standard error; Vc_{DOC}, volume of distribution of central compartment; $Vp1_{DOC}$, volume of distribution of peripheral compartment 1; $Vp2_{DOC}$, volume of distribution of peripheral compartment 2.

[a]Estimated by intravenous docetaxel and fixed in the model estimation of oral docetaxel.

We investigated whether a potential mechanism-based inhibitory effect of ritonavir on CYP3A4 could be used instead of the competitive inhibitory effect described in equation 4. This was explored by an enzyme turnover model with ritonavir inactivating CYP3A4 or accelerating the degradation rate of CYP3A4. However, these approaches failed to achieve model minimization or resulted in unreasonable parameter estimates.

The parameter estimates of the final model had adequate precision. Figures 2 and 3 show graphical model evaluations, which indicate an adequate description of the data.

Comparison of the Characteristics of Different Docetaxel Oral Formulations. The effects of the different formulations on the PK of docetaxel were estimated on absorption rate constant (k_a) and F_G. The fastest absorption was observed for the drinking solution, followed by ModraDoc001 capsule and ModraDoc006 tablet (k_a: 1.8 h^{-1} [RSE, 17%], 1.4 h^{-1} [RSE, 7%], and 1.0 h^{-1} [RSE, 10%], respectively). The drinking

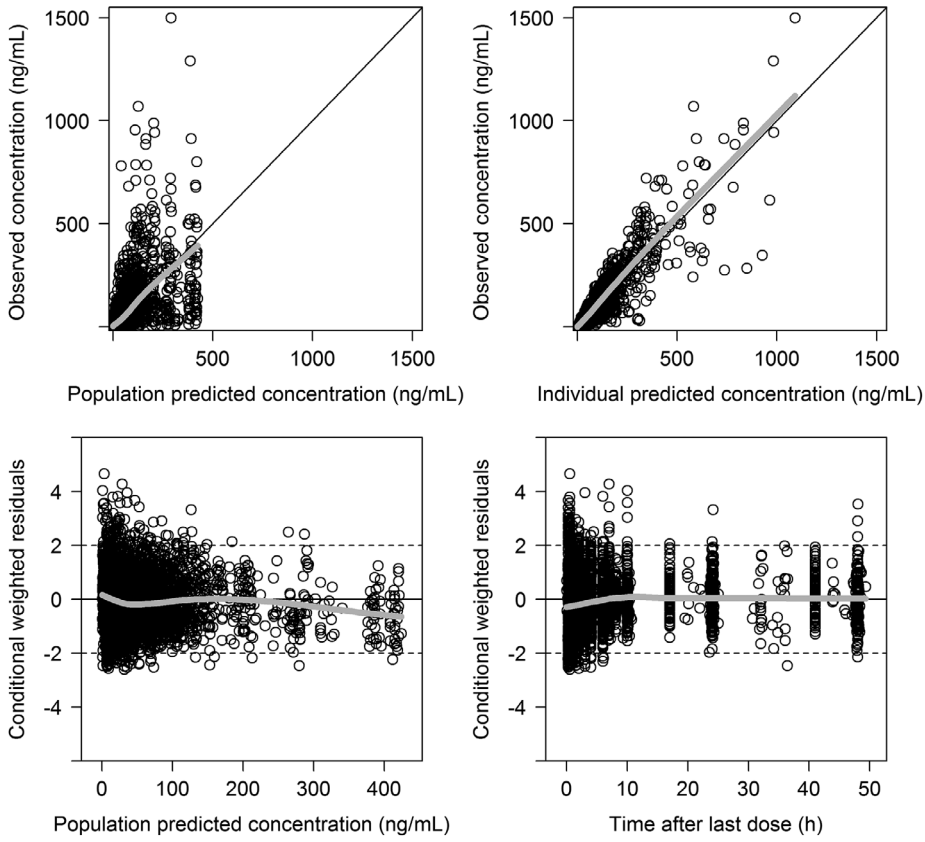

Figure 2. Goodness-of-fit plots of pharmacokinetic modelling for oral formulations of docetaxel. The plots include observed vs population predicted concentration, observed vs individual model predicted concentration, conditional weighted residuals vs population predicted concentration, and conditional weighted residuals vs time.

solution also showed the highest $F_{formulation}$ (0.27; RSE, 25%) compared to ModraDoc006 (0.22; RSE, 24%) and ModraDoc001 (0.18; RSE, 23%).

An effect of the formulation was also found on variability. The drinking solution, compared to ModraDoc formulations, showed much higher BSV (k_a: 81.7% [RSE, 18%] vs 37.3% [RSE, 16%]; F_G: 74.2% [RSE, 15%] vs 35.8% [RSE, 14%]) and higher between-day WSV (k_a: 52.4% [RSE, 13%] vs 43.1% [RSE, 12%]); F_G: 39.5% (RSE, 21%) vs 29.1% (RSE, 8%) (Table 3). The between-day and within-day WSV on F_G for ModraDoc formulations was 29.1% (RSE, 8%) and 25.2% (RSE, 21%), respectively. F_G proved to be independent from dosing frequency (once-daily dosing and twice-daily dosing) and absolute docetaxel dose administered.

Simulations

Figure 4 shows the comparison of plasma concentrations of oral docetaxel administered as a single dose and 2 doses (t = 0 and t = 7 hours) without or with ritonavir coadministration over a time span of 96 hours. The corresponding changes of docetaxel CL_{int} in ritonavir coadministration are also shown. For the docetaxel dosing regimen of once-daily 60 mg, the AUC_{96hrs} with ritonavir was 9-fold higher than docetaxel monotherapy 1204 $\mu g \cdot h/L$ vs 138 $\mu g \cdot h/L$); for the dosing regimen of twice-daily 30/20 mg, coadministration of ritonavir showed 13-fold higher AUC_{96hrs} (1458 $\mu g \cdot h/L$ vs 115 $\mu g \cdot h/L$). A single dose of 100-mg ritonavir maximally inhibited docetaxel CL_{int} to 21.8% of CL_{int0} at 3.6 hours after coadministration; twice-daily 100 mg ritonavir further inhibited the CL_{int} to 9.3% of CL_{int0} at 10.4 hours. Docetaxel CL_{int} recovered to its CL_{int0} after around 3 days. The AUC_{96hrs} of twice-daily 30/20 mg of docetaxel was higher than a once-daily 60-mg dose.

For once-daily dosing of the oral ModraDoc006-ritonavir coadministration, the median AUC_{3wks} of 60-mg docetaxel fell within the range of AUC_{3wks} of the 3 regularly used dosing regimens for IV docetaxel (Figure 5). As for the twice-daily dosing, 30/30-mg docetaxel was above the range of AUC_{3wks} of IV docetaxel, while the 20/20 regimen is within this range.

Discussion

In the current study, we developed an integrated semi-physiological PK model for ritonavir and docetaxel. Compared to the previously described PK model of oral docetaxel,[10] the current model was considerably

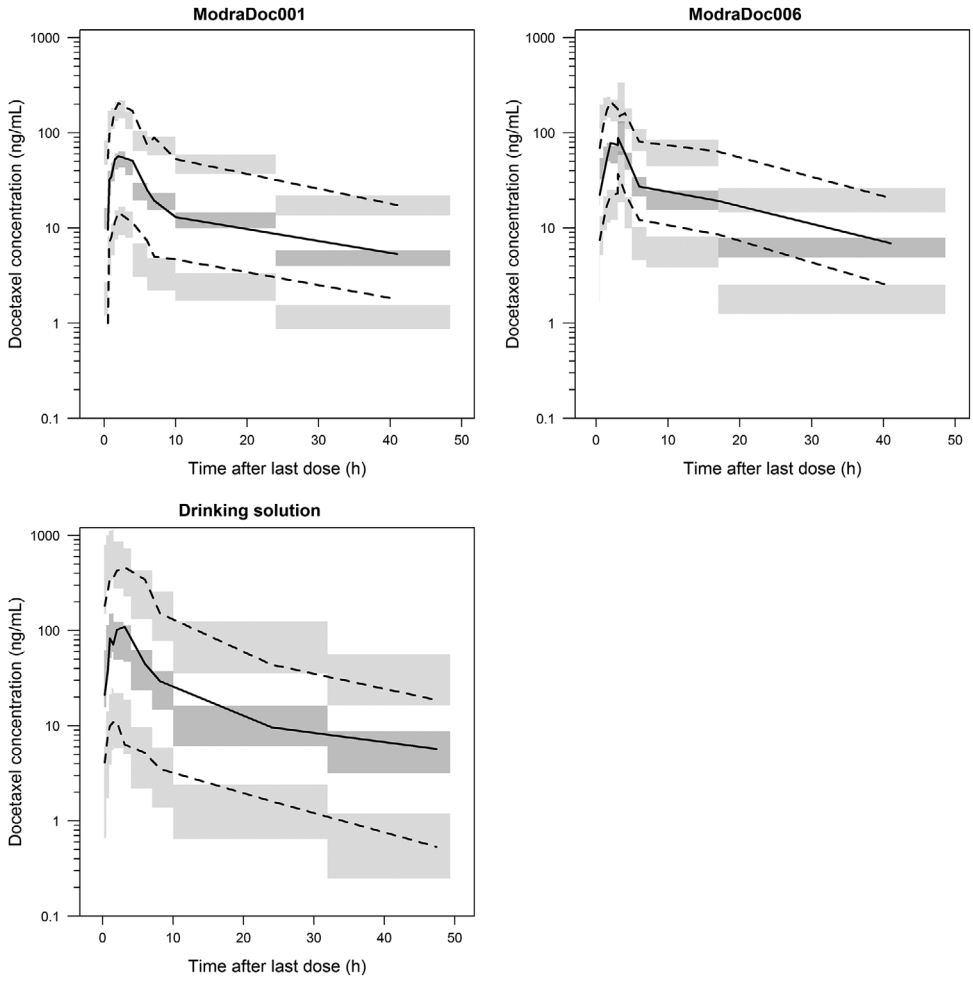

Figure 3. Visual predictive checks for docetaxel, stratified by different oral formulations (n = 1,000). Solid lines and dark gray areas represent the median observed values and simulated 95% confidence intervals. Dashed lines and light gray areas represent the 10% and 90% percentiles of the observed values and 95% confidence intervals of the simulated percentiles.

improved by incorporation of novel data. First, data on newly developed docetaxel oral formulations—ModraDoc001 capsule[6] and ModraDoc006 tablet[7]—was included, enabling further characterization of the absorption dynamics of oral docetaxel. Second, the inclusion of the data on ritonavir concentration allowed further quantification of the complex relationship between ritonavir and docetaxel PK. Third, by inclusion of the free fraction of unbound docetaxel in the well-stirred liver model, the parameters were more realistically estimated than by total docetaxel concentration.

The PK characteristics of the different docetaxel formulations were quantified. The distribution of docetaxel from the central compartment was best described by 2 peripheral compartments for the IV administration and 1 peripheral compartment for the oral formulations. As IV docetaxel is formulated in Tween80, distribution to micelles might explain this difference. The drinking solution of docetaxel was not suitable for clinical use due to its poor taste.[5] Moreover, although the F_G of the drinking solution was higher than the solid formulations, much higher BSV and WSV were observed (Table 3). The k_a of the 2 solid formulations was comparable. The F_G of ModraDoc006, however, was 16% higher than ModraDoc001. This difference is explained by the physical characteristics of these 2 formulations. The solid dispersion of ModraDoc001 was prepared by freeze drying, which did not result in a fully amorphous state, in contrast to the spray-dried formulation in ModraDoc006. The WSVs on F_G for ModraDoc formulations were relatively low (Table 3). As a result, it was decided to continue clinical trials with the ModraDoc006 tablet. With this analysis we report on the quantification of the complex PK of this oral docetaxel formulation.

The inhibitory effect of ritonavir resulted in significantly increased docetaxel plasma exposure when coadministered, especially for the twice-daily dosing regimen (Figure 4). In the twice-daily dosing regimens, an additional boost of ritonavir on the second dose was

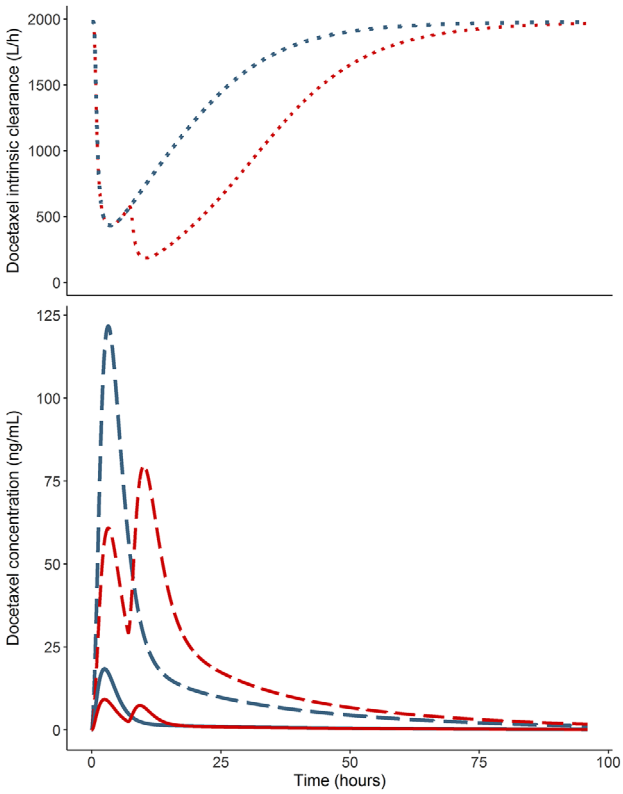

Figure 4. Simulation of population plasma concentration with corresponding intrinsic clearance of docetaxel at clinically relevant once-daily or twice-daily dosing regimens. The upper panel shows the change of docetaxel intrinsic clearance under ritonavir coadministration (dotted lines); the lower panel shows docetaxel plasma concentration without (solid lines) or with (dashed lines) ritonavir coadministration. The dosing regimens simulated in this figure are once-daily (blue graphs) 60 mg of docetaxel and twice-daily (red graphs) 30 mg followed by 20 mg of docetaxel; 100 mg of ritonavir at each intake in the coadministration.

observed, leading to a higher exposure of this regimen with the same docetaxel dose as compared to the once-daily dosing regimen.

Coadministration of the ModraDoc formulations with ritonavir at the recommended dose reached similar docetaxel exposure (AUC_{3wks}) as compared to IV docetaxel (Figure 5). In comparison, 60 mg of oral docetaxel in the once-daily dosing regimen and the regimens of 20/20 mg and 30/20 mg in the twice-daily dosing could result in clinically relevant plasma levels of docetaxel in patients.

In the current analysis, ritonavir plasma concentration was used to account for the inhibitory effect instead of ritonavir liver concentration, which may lead to a physiologically biased estimate of the inhibition constant KI. In addition, a mechanism-based inhibitory effect of ritonavir on CYP3A4 that is scientifically most reasonable[28,29] could not be identified primarily due to the scarce PK information available >24 hours after administration, which would have likely allowed estimation of kinetic changes in CYP3A4 activity. Finally, clearance routes other than the liver were not considered for docetaxel. However, even with these potential limitations, the current model sufficiently describes the observation of ritonavir and docetaxel in different formulations and allowed to support the clinical development of docetaxel-ritonavir coadministration.

The modeling and simulation supported the drug development in multiple aspects. The population approach enabled the comparison of the bioavailability between once-daily and twice-daily regimens and across the wide dose range of ModraDoc formulations. The characteristics of different formulations including BSV and WSV in absorption profiles could be quantitatively compared (Table 3). This model-based analysis also quantified the extent of the inhibitory effect of ritonavir on the metabolism of docetaxel over time (Figure 4). The magnitude of differences on the exposure between oral docetaxel with and without ritonavir coadministration could be derived from this model-based analysis. Here, the AUCs calculated from the PK model were not biased by differences in subjects at different dose levels in the clinical studies. Finally, the comparison of simulated AUCs between IV and oral docetaxel confirmed the clinical relevance of the plasma concentrations of different oral doses. The simulations showed that similar systemic exposure can be obtained by administration of oral docetaxel in combination with ritonavir.

Conclusion

We successfully developed an integrated semiphysiological PK model for docetaxel and ritonavir based on phase 1 studies of oral docetaxel coadministered with ritonavir. Compared to the drinking solution, oral ModraDoc formulations had much lower variability in plasma concentrations between and within patients. Coadministration of ritonavir resulted in exceedingly increased plasma concentrations and reduced inter- and intrapatient variability of docetaxel after administration of the oral formulations of ModraDoc, which confirmed the feasibility and necessity of coadministration in the clinic.

Conflicts of Interest

B.N., J.H.B., and J.H.M.S. are inventors and hold a patent on oral ModraDoc formulations. J.H.B. and J.H.M.S. are employees and shareholders in Modra Pharmaceuticals, a spinout company developing oral taxane formulations.

Data Sharing

The data that were used for this study cannot be shared.

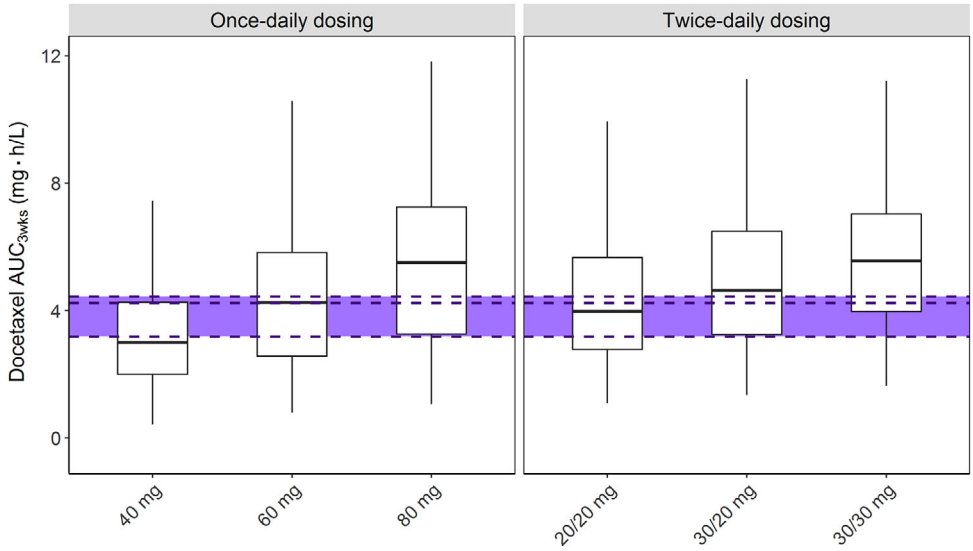

Figure 5. Comparison of docetaxel exposure between ModraDoc006 and intravenous docetaxel. The boxplot shows the median and interquartile range of simulated 3-week-time area under the concentration-time curve (AUC_{3wks}) for different dosing regimens of ModraDoc006 coadministered with ritonavir. The left panel shows once-daily dosing and the right panel twice-daily dosing. Three dashed lines from bottom to top represent the simulated AUC_{3wks} of intravenous docetaxel at dosing regimens of 3-weekly 75 mg/m^2, 3-weekly 100 mg/m^2, and weekly 35 mg/m^2, successively. The shaded area covers the range of simulated AUC_{3wks} of different dosing regimens of intravenous docetaxel.

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