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Evaluation of the linearity of docetaxel pharmacokinetics

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Abstract The taxanes, paclitaxel and docetaxel, have favorable response rates in patients with breast, gynecologic, and lung cancers and have demonstrated activity against a variety of malignancies. In human trials, paclitaxel pharmacokinetics are nonlinear and are best fit by a three-compartment model with nonlinear distribution into the second compartment as well as nonlinear elimination. This finding is important for patients receiving paclitaxel at high doses or as a short infusion, as it results in disproportionately high peak concentrations and delayed elimination. The presence of nonlinear processes in docetaxel pharmacokinetics has not previously been examined. Therefore, plasma concentration data obtained from 53 patients receiving docetaxel at 55–115 mg/m^2 over 1–24 h as part of phase I studies were modeled using the nonlinear three-compartment model found most suitable for paclitaxel and the results were compared with those obtained using the linear version. Docetaxel disposition was best described by the three-compartment nonlinear model in 28 of 53 data sets (53%). However, the difference in curve fit observed between the two models was modest (did not improve Akaike criteria) and unlikely to be of relevance. This study suggests that nonlinear processes in docetaxel pharmacokinetics may exist, but, unlike the case of paclitaxel, they are not likely to have a significant impact at the dose and administration schedule used in routine clinical practice (60–100 mg/m^2 given over 1 h by infusion). The presence of nonlinear docetaxel pharmacokinetics at doses above 115 mg/m^2 will have to be determined in case of further dose escalation.

Key words Docetaxel · Paclitaxel · Pharmacokinetics · Michaelis-Menten processes

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Introduction

The taxanes, paclitaxel and docetaxel, have had significant impact on the treatment of solid tumors, including demonstrated activity in advanced disease [8, 18]. Though the two drugs share structural similarities, distinct differences in their in vitro mechanism of action, cytotoxicity, in vivo antitumor activity, and metabolism have been noted [13, 14, 19].

Clinical pharmacology studies of both paclitaxel and docetaxel have described sigmoidal relationships between the area under the concentration-time curve (AUC) or time above 0.05 μM and hematologic toxicity [4, 7, 10, 11]. In addition, docetaxel exposure during the first cycle is an independent predictor of both safety (incidence of febrile neuropenia) and efficacy (time to progression in non-small-cell lung cancer) [6]. This has stimulated interest in population pharmacokinetic analysis on which prospective concentration-controlled trials could be based. Preclinical and early clinical studies used two- and three-compartment linear models to describe paclitaxel pharmacokinetics. However, more extensive analysis found Michaelis-Menten processes governing both distribution into a second compartment and elimination from the central compartment [11, 15]. This finding has significant clinical implications in that (1) a greater than expected increase in patients' paclitaxel systemic exposure will result from a given increase in dose – for example, in patients receiving a 3-h

paclitaxel infusion a 30% dose increase from 135 to 175 mg/m^2 has resulted in an 80% increase in AUC [11] – and (2) it is responsible for the schedule dependency of paclitaxel pharmacokinetics, whereby nonlinear features are more apparent with shorter administration schedules.

Pharmacokinetics studies carried out to date have found docetaxel disposition to be best described by a three-compartment linear model [5, 12]. However, nonlinear models have not been evaluated for docetaxel. As myelosuppression is the primary dose-limiting toxicity observed, docetaxel dose escalation with hematopoietic support is being considered. An increased dose in the context of nonlinear drug disposition can lead to significant clinical problems, as has been found for paclitaxel. Therefore, we explored linear and nonlinear three-compartment pharmacokinetic models to examine the linearity of plasma docetaxel disposition.

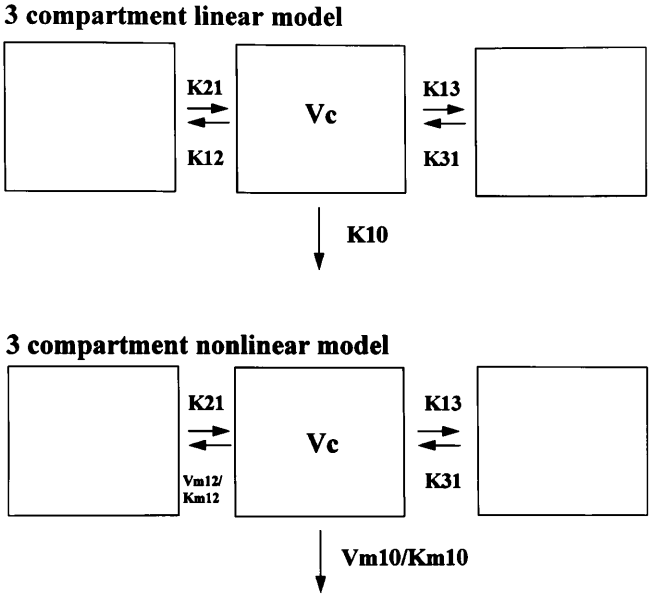

Fig. 1 Linear and nonlinear three-compartment pharmacokinetic models

Patients and methods

Patient population

The data sets for pharmacokinetic analysis were selected from previous phase I studies of docetaxel in patients with solid tumors [1, 4, 7, 10]. Only patients for whom complete plasma concentration-time information was available during the infusion and at least 8 h after the end of the infusion were included in the analysis. This criterion confined the study to patients receiving the top three docetaxel dose levels in each trial. Patients were treated at five clinical centers: San Antonio, Texas, USA; Paris and Lyon, France; Geneva, Switzerland; and Glasgow, UK. The specific blood-sampling times have been detailed previously [1, 4, 7, 10]. In all, 7–18 plasma samples were obtained from each subject over the study period; this included a minimum of 1 and a maximum of 7 samples taken prior to the end of the infusion. Plasma docetaxel was analyzed at each center by high-performance liquid chromatography (HPLC) with UV detection using the same previously described method [17].

Pharmacokinetic analysis

The pharmacokinetics of docetaxel were evaluated using a three-compartment model with linear distribution and elimination processes and a three-compartment model with Michaelis-Menten processes governing both distribution into the second compartment and elimination from the central compartment (Fig. 1) [11]. Therefore, the parameters estimated in the linear model included Vc, K12, K21, K13, K31, and K10, whereas the following parameters were estimated in the nonlinear model: Vc, Vmax$_{12}$, Km$_{12}$, K21, K13, K31, Vmax$_{10}$, and Km$_{10}$. An iterative two-stage analysis was implemented on ADAPT II software [9]. An initial run was conducted using maximum-likelihood estimation, and the mean and interpatient coefficient of variation (CV) results were used to construct a diagonal covariance matrix for use in a Bayesian algorithm. The Bayesian analysis was repeated with an updated covariance matrix until stable estimates of the mean parameter estimates for all parameters were obtained. Each observation was weighted by the inverse of an estimate of the variance for the predicted values for both models. Goodness of model-curve fit was assessed by the Akaike information criterion (AIC) [2]. The bias (percentage of mean prediction error, %ME) and precision (percentage of root mean square error, %RMSE) was also used to assess the goodness of fit of each model. Systemic clearance for the linear model was calculated as $Vc \times$ K10. The docetaxel AUC was estimated as the dose divided by the systemic clearance. Differences observed in pharmacokinetic parameter estimates between the various doses and durations of infusion were assessed by the Kruskal-Wallis or Mann-Whitney test. The statistical significance of differences in the AIC value recorded for the linear and nonlinear model within each patient were assessed by the Wilcoxon test.

Results

A total of 53 patient data sets were used for pharmacokinetic analysis. The docetaxel dose ranged from 55 to 115 mg/m^2 given over 1–24 h (Table 1). Each of the 6- and 24-h cohorts consisted of patients from specific study centers, whereas the 1-, 2-, and 3-h cohorts were accrued from four separate study centers. Bayesian analysis was updated and repeated until stable estimates of the mean pharmacokinetic parameters were obtained. This required six iterations for the nonlinear model and seven iterations for the linear model. The estimated mean value and CV recorded for each pharmacokinetic parameter are listed in Table 2. The goodness-of-curve fit was similar for the nonlinear model (median AIC value −9.0, range −34.7 to 31.1) and the linear model (median AIC value −7.7, range −36.7 to 64.6). The AIC values noted for the two models were not significantly

Table 1 Docetaxel administration information

Dose (mg/m^2)	n	Infusion length (hours)	n
55	3	1	13
70	6	2	17
80–90	12	3	4
100	26	6	8
115	6	24	11

Table 2 Final parameter estimates recorded for the linear and nonlinear models

3-compartment linear model			3-compartment nonlinear model		
	Mean	%CV		Mean	%CV
Vc (ml/m^2)	4,084	35.7	Vc (ml/m^2)	2,629	49.0
$K12$ (h^{-1})	1.32	33.7	$Vmax_{12}$ (ng/h)	11,640	54.9
$K21$ (h^{-1})	0.92	28.4	Km_{12} (ng/ml)	1,616	42.2
$K13$ (h^{-1})	1.046	46.7	$K21$ (h^{-1})	1.634	48.5
$K31$ (h^{-1})	0.05	26.0	$K13$ (h^{-1})	7.66	44.8
$K10$ (h^{-1})	5.17	41.8	$K31$ (h^{-1})	0.044	57.0
			$Vmax_{10}$ (ng/h)	1,551	59.0
			Km_{10} (ng/ml)	28.6	45.8

different (Wilcoxon test, $P = 0.16$). The nonlinear model provided a more precise and less biased fit of individual data points than did the linear model (Tables 3, 4). The improved goodness of fit was greatest for time points up to the end of the infusion (Fig. 2, Table 3), whereas the two models performed similarly in the postinfusion elimination profile. In the linear model, neither Vc, $K12$, $K21$, $K13$, $K31$, nor $K10$ estimates were significantly influenced by the docetaxel dose. The estimate of the docetaxel AUC was linearly related to the dose, and a large degree of variability in AUC was observed at all doses given. For example, a 2.3-fold range of AUC values was observed among the 13 patients who received docetaxel at 100 mg/m^2 over 1–2 h, the dose commonly used in clinical trials (range 3.55–8.29 μg ml^{-1} h; median 5.22 μg ml^{-1} h).

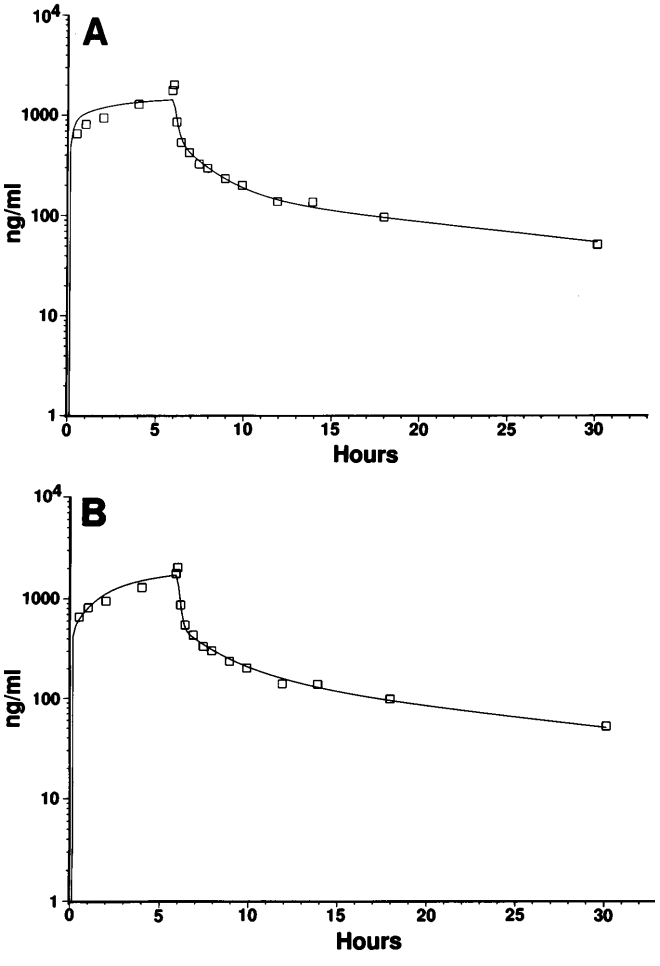

Fig. 2A,B Pharmacokinetic profile of a patient receiving docetaxel at 100 mg/m^2 over 6 h as fit by the **A** linear and **B** nonlinear models

Discussion

The finding of clinically significant nonlinear processes in paclitaxel distribution and elimination and their contribution to toxicity provides the impetus to investigate such processes in docetaxel [11, 15]. Pharmacokinetic modeling of docetaxel plasma concentration-time profiles was therefore performed using the three-compartment model found most appropriate for paclitaxel over a variety of doses and infusion schedules [11]. The data obtained from 53 patients receiving docetaxel at 55–115 mg/m^2 as a 1-, 2-, 3-, 6-, or 24-h infusion suggest the presence of nonlinear pharmacokinetic processes. The overall measures of model fit were better for the nonlinear model than for the linear model, with the greatest differences being seen for plasma samples obtained prior to the end of the infusion (Table 3). However, it should be noted that improvement of the fit did not result in overall improvement of the Akaike criteria, since the nonlinear model involved two more parameters than did the linear model. Moreover, the impact of these processes is modest at best at the docetaxel doses examined in this analysis.

Unlike the case of paclitaxel, instability in model parameters with increasing dose was not observed for docetaxel with the linear model [11]. The median absolute difference in predicted-actual plasma concentration was small for both the linear (−0.28 ng/ml) and nonlinear (−0.17 ng/ml) models. The level of model bias (−5%) and precision (38%) found for the three-compartment linear model was acceptable for clinical pharmacokinetic analysis, particularly for docetaxel given as a 1-h infusion, whereby the nonlinear processes are less apparent. In addition, nonlinear processes were graphically evident in only six patients (gradual increase in plasma concentration during the infusion with rapid postinfusion elimination; Fig. 2) and, hence, were not observed in the majority of patients (Table 4). Indeed, the nonlinear model improved the goodness of fit for

Table 3 Bias and precision of model fit to docetaxel plasma concentrations

	%ME (bias)	%RMSE (precision)
All data points:		
3-Compartment linear model	−5.14	37.78
3-Compartment nonlinear model	−2.38	13.72
Data through the end of infusion only:		
3-Compartment linear model	−12.84	70.02
3-Compartment nonlinear model	−2.8	18.74
Postinfusion data only:		
3-Compartment linear model	−2.54	15.91
3-Compartment nonlinear model	−2.04	12.11

Table 4 Proportion of data sets best fit by the nonlinear pharmacokinetic model

1-h Infusion	4/13	(31%)
2-h Infusion	7/17	(41%)
3-h Infusion	3/4	(75%)
6-h Infusion	6/8	(75%)
24-h Infusion	8/11	(73%)
Total	28/53	(53%)

only 31% of patients receiving the 1-h infusion (Table 4). The large CV observed for parameters from the nonlinear model (Table 2) suggest instability of the estimates and support the appropriateness of the linear model.

Taxane pharmacokinetics may also be influenced by the pharmaceutical vehicle used in the clinical preparation. Paclitaxel is formulated in 50% Cremophor EL and 50% dehydrated alcohol to overcome difficulties with solubility in intravenous fluids, whereas docetaxel is formulated in 100% polysorbate 80 with an ethanol-containing diluent (13% w/w). Cremophor EL appears to influence nonlinear paclitaxel systemic clearance in mice and may contribute to the more striking nonlinearity found for paclitaxel as compared with docetaxel in humans [16]. Preclinical evaluation of docetaxel pharmacokinetics has demonstrated linearity within the range of "pharmacological" doses [3]. Nonlinearity was observed at the highest dose tested, which was also associated with significant toxicity [3].

The pharmacokinetic parameter estimates obtained for docetaxel using the linear model and the iterative two-stage approach were consistent with recent nonlinear mixed-effect modeling (NONMEM) analyses [5, 12]. Although these NONMEM analyses used data obtained from patients receiving a 1- to 2-h infusion of docetaxel (up to 547 patients) and the current study included 1-, 2-, 3-, 6-, and 24-h infusions, both the mean population values and the CV of parameter estimates from the three-compartment linear model were similar between the two methods.

In summary, docetaxel pharmacokinetic analysis may suggest the presence of nonlinear pathways. In contrast to the case of paclitaxel, this nonlinearity does not appear to be clinically important at currently used dose regimens (i.e., 60–100 mg/m^2 given i.v. over 1 h). However, great care should be taken in future studies of docetaxel dose escalation, such as those involving bone marrow transplantation with hematopoietic support, where a greater than expected increase in patients' systemic exposure could result from a given increase in the docetaxel dose.

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References

1. Aapro MS, Zulian G, Alberto P, Bruno R, Oulid-Aissa D, Le Bail N (1992) Phase I and pharmacokinetic study of RP 56976 in a new ethanol-free formulation of Taxotere. Ann Oncol 3: 53
2. Akaike H (1976) An information criterion (AIC). Math Sci 14: 5
3. Bissery MC, Nohynek G, Sanderink GJ, Lavelle F (1995) Docetaxel (Taxotere): a review of preclinical and clinical experience. I. Preclinical experience. Anticancer Drugs 6: 339
4. Bissett D, Setanoians A, Cassidy J, Graham MA, Chadwick GA, Wilson P, Auzannet V, LeBail N, Kaye SB, Kerr DJ (1993) Phase I and pharmacokinetic study of taxotere (RP 56976) administered as a 24-hour infusion. Cancer Res 53: 523
5. Bruno R, Vivier N, Vergniol JC, De Phillips SL, Montay G, Sheiner LB (1996) A population pharmacokinetic model for docetaxel (Taxotere): model building and validation. J Pharmacokinet Biopharm 24: 153
6. Bruno R, Hille D, Riva A, Vivier N, Bokkel Huinink WW ten, Oosterom AT van, Kaye SB, Verweij J, Fossella FV, Valero V, Rigas JR, Seidman AD, Chevallier B, Fumoleau P, Burris HA, Ravdin PM, Sheiner LB (1998) Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies. J Clin Oncol 16: 187
7. Burris H, Irvin R, Kuhn J, Kalter S, Smith L, Shaffer D, Fields S, Weiss G, Eckardt J, Rodriguez G, Rinaldi D, Wall J, Cook G, Smith S, Vreeland F, Bayssas M, LeBail N, Von Hoff D (1993) Phase I clinical trial of taxotere administered as either a 2-hour or 6-hour intravenous infusion. J Clin Oncol 11: 950
8. Chevallier B, Fumoleau P, Kerbrat P, Dieras V, Roche H, Krakowski I, Azli N, Bayssas M, Lentz MA, Van Glabbeke M (1995) Docetaxel is a major cytotoxic drug for the treatment of advanced breast cancer: a phase II trial of the Clinical Screening Cooperative Group of the European Organization for Research and Treatment of Cancer. J Clin Oncol 13: 314
9. D'Argenio DZ, Schumitzky A (1979) A program package for simulation and parameter estimation in pharmacokinetic systems. Comput Prog Biomed 9: 115
10. Extra J-M, Rousseau F, Bruno R, Clavel M, LeBail M, Marty M (1993) Phase I and pharmacokinetic study of Taxotere (RP 56976; NSC 628503) given as a short intravenous infusion. Cancer Res 53: 1037

11. Kearns CM, Giani L, Egorin MJ (1995) Paclitaxel pharmacokinetics and pharmacodynamics. Semin Oncol 22 [Suppl 6]: 16
12. Launay Iliadis MC, Bruno R, Cosson V, Vergniol JC, Oulid Aissa D, Marty M, Clavel M, Aapro M, Le Bail N, Iliadis A (1995) Population pharmacokinetics of docetaxel during phase I studies using nonlinear mixed effect modeling and nonparametric maximum likelihood estimation. Cancer Chemother Pharmacol 37: 47
13. Marre F, Sanderink G-J, Sousa G de, Gaillard C, Martinet M, Rahmani R (1996) Hepatic biotransformation of docetaxel (Taxotere) in vitro: involvement of the CYP3A subfamily in humans. Cancer Res 56: 1296
14. Rahman A, Korzekwa KR, Grogan J, Gonzalez FJ, Harris JW (1994) Selective biotransformation of taxol to 6α-hydroxytaxol by human cytochrome P450 2C8. Cancer Res 54: 5543
15. Sonnichsen DS, Hurwitz CA, Pratt CB, Shuster JJ, Relling MV (1994) Saturable pharmacokinetics and paclitaxel pharmacodynamics in children with solid tumors. J Clin Oncol 12: 532
16. Sparreboom A, Tellingen O van, Nooijen WJ, Beijnen JH (1996) Nonlinear pharmacokinetics of paclitaxel in mice results from the pharmaceutical vehicle Cremophor EL. Cancer Res 56: 2112
17. Vergniol JC, Bruno R, Montay G, Frydman A (1992) Determination of Taxotere in human plasma by a semi-automated high-performance liquid chromatographic method. J Chromatogr 582: 273
18. Verweij J (1994) Docetaxel (Taxotere): a new anti-cancer drug with promising potential? Br J Cancer 70: 183
19. Verweij J, Clavel M, Chevallier B (1994) Paclitaxel (Taxol) and docetaxel (Taxotere): not simply two of a kind. Ann Oncol 5: 495