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SHORT COMMUNICATION

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Pharmacokinetics of paclitaxel in an anephric patient

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Abstract *Purpose*: To assess the pharmacokinetics of paclitaxel for recurrent Wilms' tumor in an anephric pediatric patient receiving hemodialysis. *Methods*: Paclitaxel was administered at a dose of 250 mg/m^2 and 350 mg/m^2 by 24-h continuous intravenous (IV) infusion as two consecutive courses, respectively, separated by approximately 3 weeks. Paclitaxel plasma concentrations were measured by high-performance liquid chromatography (HPLC). *Results*: Paclitaxel disposition was comparable to that reported in similarly treated children with normal renal function. For the first course (250 mg/m^2), paclitaxel concentrations were best fit by a two-compartment, first-order model. The calculated pharmacokinetic parameters were 0.312 h^{-1} for the first-order rate constant of elimination (K_e), 52.4 l/m^2 for the apparent volume of distribution (V_c), 0.170 h^{-1} and 0.105 h^{-1} for the first-order rate constants for transit from central to peripheral compartments (K_{cp}) and peripheral to central compartments (K_{pc}), respectively, 16.9 $\mu M \cdot$ h for the area under the plasma concentration-versus-time curve (AUC), and 273 ml/min per m^2 for average clearance (Cl). The concentration-versus-time data with the second course (at the higher dosage of 350 mg/m^2) were better described by a two-compartment model with saturable elimination. The calculated pharmacokinetic parameters were 12.0 μmol $\cdot$ h^{-1} for the maximal rate of elimination (Vm_{1-0}), 0.158 μM for the concentration at which the rate of elimination is 50% of maximal (Km_{1-0}), 0.809 h^{-1} for K_{cp}, 0.0792 h^{-1} for K_{pc}, 23.5 l/m^2 for V_c, 20.9 $\mu M \cdot$ h for AUC, and 327 ml/min per m^2 for Cl. Paclitaxel was undetectable in the dialysate. *Conclusions*: The level of systemic exposure in our anephric patient was comparable to or lower than that achieved in patients with normal renal function at similar dosages. The patient tolerated therapy without problems. It appears that pediatric patients in renal failure can be treated with paclitaxel as a 24-h continuous infusion at doses similar to those used in patients with normal renal function.

Key words Paclitaxel · Pharmacokinetics · Renal failure · Hemodialysis · Nifedipine

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Introduction

Paclitaxel was discovered in a crude extract from the bark of the Pacific yew *Taxus brevifolia*. It has a unique cytotoxic mechanism: it promotes the polymerization of intracellular tubulin and stabilizes abnormal microtubule structures against depolymerization, thereby disrupting cell division and interphase processes. Paclitaxel, either as a single agent or in combination with other cytotoxic drugs, has been shown to have activity in a number of solid tumors, including ovarian, breast, lung, head and neck, testicular, bladder, and esophageal cancers. Paclitaxel is extensively metabolized by hepatic cytochromes P450 [3, 9, 12, 15, 22] and secreted in bile, with only 4.3 to 8.2% excreted unchanged by the kidneys [1, 7, 23]. Data reported in abstract form [4, 19] indicate clearances of 113–277 ml/min per m^2 following 3-h paclitaxel infusions in two adults on hemodialysis,

values which correspond to low-to-average clearances in patients without renal failure [16, 17, 24]. There are no published data on paclitaxel disposition in children with renal failure. We describe the clinical course and pharmacokinetics of paclitaxel in an anephric pediatric patient on chronic hemodialysis with recurrent, metastatic Wilms' tumor who was treated with two courses of paclitaxel at doses of 250 mg/m^2 and 350 mg/m^2, respectively, given as 24-h continuous IV infusions.

Case report

A Caucasian female was initially diagnosed with bilateral (stage V) Wilms' tumor at 6 years of age. Histology was favorable and the tumor did not extend beyond the renal capsule. Treatment included left nephrectomy and right partial nephrectomy followed by chemotherapy consisting of vincristine and actinomycin D for 65 weeks. Local relapse and bilateral lung metastases occurred about one year after the completion of therapy. Pathology at relapse was consistent with diffuse anaplastic Wilms' tumor. The patient received two courses of chemotherapy containing two cycles of cyclophosphamide and etoposide and two cycles of carboplatin and etoposide, which resulted in radiologic resolution of pulmonary metastases and 33% reduction of the renal mass. However, patient evaluation 2 months later showed a recurrence of pulmonary metastases and an increase in renal mass.

The patient underwent salvage therapy with pulmonary metastasectomy, whole lung irradiation, one cycle of doxorubicin and ifosfamide, one cycle of vincristine, ifosfamide, and etoposide, and one cycle of vincristine, actinomycin D, and doxorubicin. The child underwent a complete right nephrectomy and irradiation to the renal bed and regional lymph node area, but computed tomography scan revealed recurrent nodules in both lungs. It was decided to administer a first course of paclitaxel at a dose of 250 mg/m^2 as a 24-h continuous IV infusion on a nondialysis day, a dose lower than the Pediatric Oncology Group (POG) recommended phase II dose [11] of 350 mg/m^2 because of the previous heavy vincristine use and concerns regarding the risk for neurotoxicity [21], particularly given the patient's anephric state. A premedication regimen of dexamethasone and diphenhydramine was used to prevent acute hypersensitivity reactions. Based on the calculated pharmacokinetic parameters and the absence of adverse effects during the first course of therapy, the second course of paclitaxel consisted of an augmented dose of 350 mg/m^2 infused over 24 h, 24 days after the first course.

Heparinized venous blood samples were obtained before paclitaxel administration, and 2, 8, 23, 25, 26, 28, and 48 h from the start of infusion. Samples were also collected before, during, and after dialysis, which started 36.8 and 41.6 h after the beginning of infusion for each course, respectively. Samples were centrifuged at 3000 rpm for 5 min and the plasma was frozen at −80 °C immediately for later analysis. Plasma and dialysate paclitaxel concentrations were measured using a high-performance liquid chromatography-ultraviolet (HPLC-UV) method [22]. Pharmacokinetic modeling of the plasma concentration-versus-time data sets was performed using the ADAPT II software package (Biomedical Simulations Resource, University of Southern California, Los Angeles, Calif.) with Bayesian estimation algorithms. A model incorporating saturable distribution and elimination [21] was used first to fit the data. Because of surprisingly low plasma concentrations and poor model fits, alternative models incorporating first-order processes were also evaluated. It should be acknowledged that paclitaxel "clearance" is an "average" clearance applied to the entire concentration-versus-time curve, due to possible concentration dependence.

Results and discussion

The paclitaxel plasma concentrations during and following 24-h continuous IV infusions of 250 mg/m^2 and 350 mg/m^2 are shown in Fig. 1A and Fig. 1B, respectively. The apparent clearances in this anephric patient (273 and 327 ml/min per m^2 for courses no. 1 and no. 2, respectively) are within the range of those observed in both adult (102 to 359 ml/min per m^2) [16, 17, 24] and pediatric (72 to 518 ml/min per m^2) [21] patients without kidney dysfunction. The AUCs of 16.9 and 20.9 $\mu M \cdot$ h for the two courses were similar to pediatric [21] and adult [24] patients with normal renal function. Figure 1 shows the similarity between the plasma concentrations in this patient compared with those predicted from pediatric patients with normal renal function, based on parameters estimated in children treated at identical dosages [21].

The most parsimonious model to characterize paclitaxel disposition is a two-compartment, first-order model at lower dosages or in patients with fast clearances [1, 23, 24]. However, the higher concentrations achieved with higher doses [21], shorter infusions, or in patients with poor clearance require a model combining saturable distribution and saturable elimination. The latter model accounts for the overestimation of early during-infusion plasma concentrations by first-order models (saturable distribution) and the inverse relationship between paclitaxel clearance and dosage (saturable elimination) seen in children with refractory solid tumors [21] and in some adults [6, 10, 14, 17, 20] with normal renal function. In our anephric patient given 250 mg/m^2 (lower than the recommended dose for phase II studies in children), the data were best fit by a first-order model, but data with the higher dosage of 350 mg/m^2 were best fit with a model incorporating saturable elimination, as evident by the lowest Akaike Information

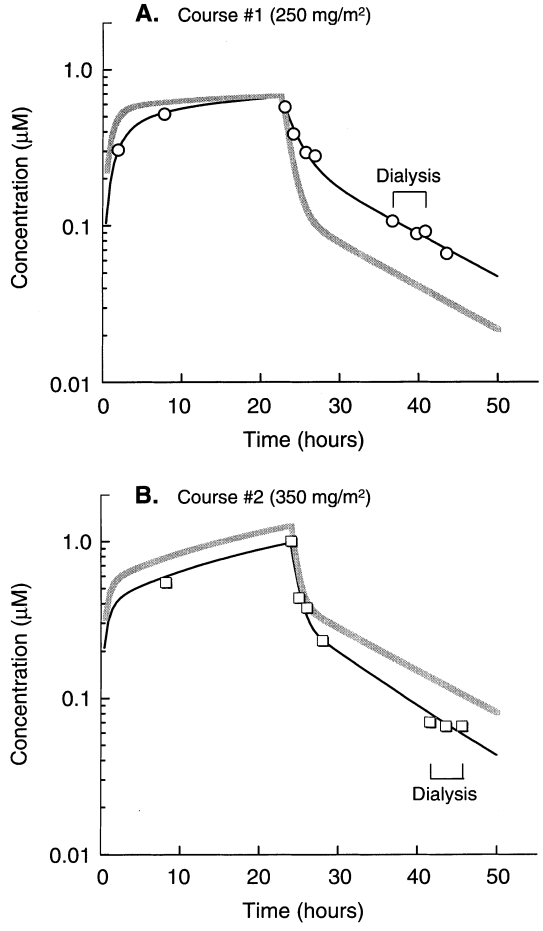

Fig. 1A,B Paclitaxel plasma concentration-versus-time profiles for **(A)** course no. 1 (250 mg/m^2) (○) and **(B)** course no. 2 (350 mg/m^2) (□). The symbols represent measured paclitaxel plasma concentrations and the lines represent the best-fit curves using Bayesian estimation algorithms for a two-compartment model (course no. 1) and a two-compartment model with saturable elimination (course no. 2). The *thick gray lines* are simulated concentrations based on measured median pharmacokinetic parameters [21] estimated in children with normal renal function given doses, identical to those given to the anephric patient. Brackets indicate the time period during which the patient underwent hemodialysis

Table 1 Comparison of goodness-of-fit for four paclitaxel pharmacokinetic models (*better fits are indicated by lower Akaike Information Criterion values with best fit)

Pharmacokinetic model	Akaike Information Criterion* (course no. 1)	Akaike Information Criterion* (course no. 2)
Two-compartment, first-order	*−69.444*	−42.824
Two-compartment with saturable distribution	−60.522	−35.344
Two-compartment with saturable elimination	−66.708	*−47.231*
Two-compartment with saturable distribution and elimination	−57.741	−35.805

Table 2 Summary of pharmacokinetic parameters (course no. 1): two-compartment, first order model

Parameter		CV (%)
K_e (h^{-1})	0.312	14.1
V_c (l/m^2)	52.4	14.4
K_{cp} (h^{-1})	0.170	35.2
K_{pc} (h^{-1})	0.105	30.3
AUC $\mu M \cdot h$)	16.9	
Dose/AUC (ml/min per m^2)	273	

Table 3 Summary of pharmacokinetic parameters (course no. 2): two-compartment model with saturable elimination

Parameter		CV (%)
Vm_{1-0} ($\mu mol \cdot h^{-1}$)	12.0	11.1
Km_{1-0} (μM)	0.158	28.7
V_c (l/m^2)	23.5	25.3
K_{cp} (h^{-1})	0.809	26.3
K_{pc} (h^{-1})	0.0792	14.0
AUC ($\mu M \cdot h$)	20.9	
Dose/AUC (ml/min per m^2)	327	

Criterion values (Table 1). We also modeled both courses of therapy simultaneously, using each of the four models indicated in Table 1. Although the lowest Akaike Information Criterion value was achieved with the saturable distribution model, modeling each course individually resulted in a better fit to the data, as determined by sum of squares, coefficients of determination, and visual inspection of the data (data not shown).

Estimated pharmacokinetic parameters for the first and second courses are listed in Tables 2 and 3, respectively. The peak plasma concentrations (C_{max}) for the two courses were 0.572 μM and 1.00 μM, respectively, which were lower than those reported in adults (mean ± SE, 1.57 ± 0.29 μM at 250 mg/m^2) [16], but similar to those in children [median (range), 0.71 μM (0.35–1.34) at 250 mg/m^2 and 1.73 μM (0.43–3.02) at 350 mg/m^2] with normal renal function receiving paclitaxel as an infusion over 24 h [21]. The apparent volumes of distribution (V_c) (52.4 and 23.5 l/m^2) were more comparable to values reported in adults (11.58–237 l/m^2) [1, 23, 24] than to those reported in children (2.9–20.0 l/m^2) [21] with normal renal function, despite large interpatient variability. A lower C_{max}, despite a similar V_c, may indicate a more rapid initial paclitaxel distribution in our pediatric patient on hemodialysis than in adult patients with normal renal function. Despite the fact that average clearance for the first course (273 ml/min per m^2) was lower than that for the second course (327 ml/min per m^2), a model incorporating saturable elimination resulted in a lower Akaike Information Criterion value (Table 1) than a first-order model applied at the higher dose given with the second course.

The 20% increase in average clearance observed with the second course was somewhat unexpected given that clearance should decrease as dose increases. Paclitaxel systemic clearance decreased from 321 ml/min per m^2 at 250 mg/m^2 to 141 ml/min per m^2 at 350 mg/m^2 in pediatric patients with normal renal function [21]. We speculate that the lower average clearance with the first course may have been the result of a drug interaction. Nifedipine, which is metabolized by CYP3A4 [8], was administered before and during the first course of paclitaxel infusion (total of six doses). CYP3A4 can predominate in paclitaxel metabolism and coadministration of a CYP3A4 substrate, fluconazole, was associated with decreased paclitaxel clearance [22]. Moreover, paclitaxel and nifedipine interact with P-glycoprotein [5, 18]. Thus, competition for metabolism and/or elimination could have slowed paclitaxel clearance during the first course.

Dialysate samples were collected 39.8 and 43.6 h from the start of infusion of each respective treatment course for measurement of paclitaxel concentration, but none was detected. The limit of detection of our assay, defined as a signal-to-noise ratio of three, was 0.02 μM. Therefore, with the plasma concentrations of 0.088 to 0.066 μM at this time, at least 30% of the drug would have had to be removed by hemodialysis in order to be quantitated in the dialysate. Based on paclitaxel's large volume of distribution, high plasma-protein binding, our data, and a prior preliminary report [19], paclitaxel is likely to be poorly dialyzable.

Both elevated serum creatinine and higher paclitaxel AUC correlated with the occurrence of nonhematologic toxicities in children [21], despite only a small fraction of paclitaxel undergoing renal elimination [9, 13, 24]. The median AUCs in children who experience neurotoxicity or musculoskeletal toxicity were 54 $\mu M \cdot$ h (range 22–115 $\mu M \cdot$ h) and 71 $\mu M \cdot$ h (range 15–92 $\mu M \cdot$ h), respectively, while those children with no toxicity had a median AUC of 30 $\mu M \cdot$ h (range 9–90 $\mu M \cdot$ h) [21]. Our patient tolerated both courses without problems, despite elevated serum creatinine levels of 3.2 and 7.3 mg/dl before each course of paclitaxel, respectively. However, the AUCs for both treatment courses (16.9 and 20.9 $\mu M \cdot$ h) were well below the medians associated with toxicity in our prior pediatric study.

Previous experiences of paclitaxel infused over 3 h in adult patients with renal impairment indicated that pharmacokinetic parameters [2, 4, 19] and mean percentage decrease in neutrophils [2] were within the range of those defined in patients with normal renal function. In addition, our data further suggest that the pharmacokinetics of paclitaxel are not altered in patients with renal failure. Caveats are that the dosages were not unusually high (250 and 350 mg/m^2) and were administered over 24 h. It is possible that hepatic biotransformation pathways could become saturated with higher dosages and/or shorter infusions, particularly if concurrent drugs are given which inhibit paclitaxel's metabolism or elimination. Hemodialysis did not remove paclitaxel from blood. Because this patient exhibited neither altered pharmacokinetics nor pharmacodynamics of paclitaxel, it appears that no dosage alteration for 24-h infusions of paclitaxel at these dosage levels is required on the basis of renal failure alone.

References

1. Brown T, Havlin K, Weiss G, Cagnola J, Koeller J, Kuhn J, Rizzo J, Craig J, Philips J, Von Hoff D (1991) A phase I trial of taxol given by a 6-hour intravenous infusion. J Clin Oncol 9: 1261
2. Conley BA, Zaharski D, Kearns CM, Rosen DM, Van Echo DA, Egorin MJ (1997) Paclitaxel (P) pharmacokinetic (PK)/pharmacodynamic (PD) relationships in patients (pts) with renal dysfunction (RD). Proc Annu Meet Am Soc Clin Oncol 16: 233a, abstract 819
3. Cresteil T, Monsarrat B, Alvinerie P, Tréluyer JM, Vieira I, Wright M (1994) Taxol metabolism by human liver microsomes: identification of cytochrome P450 isozymes involved in its biotransformation. Cancer Res 54: 386
4. Fazeny B, Olsen SJ, Willey T, Stewart MB, Dittrich E, Huber H, Dittrich C (1995) Pharmacokinetic assessment of paclitaxel in an ovarian cancer patient on hemodialysis. Proc Annu Meet Am Soc Clin Oncol 14: 173 Abstract 375
5. Fedeli L, Colozza M, Boschetti E, Sabalich I, Aristei C, Guerciolini R, Del Favero A, Rossetti R, Tonato M, Rambotti P, Davis S (1989) Pharmacokinetics of vincristine in cancer patients treated with nifedipine. Cancer 64: 1805
6. Gianni L, Kearns CM, Giani A, Capri G, Viganó L, Locatelli A, Bonadonna G, Egorin M (1995) Nonlinear pharmacokinetics and metabolism of paclitaxel and its pharmacokinetic/pharmacodynamic relationships in humans. J Clin Oncol 13: 180
7. Grem JL, Tutsch KD, Simon KJ, Alberti DB, Willson JKV, Tormey DC, Swaminathan S, Trump DL (1987) Phase I study of taxol administered as a short iv infusion daily for 5 days. Cancer Treat Rep 71: 1179
8. Guengerich FP, Brian WR, Iwasaki M, Sari M-A, Bäärnhielm C, Berntsson P (1991) Oxidation of dihydropyridine calcium channel blockers and analogues by human liver cytochrome P-450 IIIA4. J Med Chem 34: 1838
9. Harris JW, Rahman A, Kim B-R, Guengerich FP, Collins JM (1994) Metabolism of taxol by human hepatic microsomes and liver slices: participation of cytochrome P450 3A4 and an unknown P450 enzyme. Cancer Res 54: 4026
10. Huizing MT, Keung ACF, Rosing H, van der Kuij V, ten Bokkel Huinink WW, Mandjes IM, Dubbelman AC, Pinedo HM, Beijnen JH (1993) Pharmacokinetics of paclitaxel and metabolites in a randomized cooperative study in platinum-pretreated ovarian cancer patients. J Clin Oncol 11: 2127
11. Hurwitz CA, Relling MV, Weitman SD, Ravindranath Y, Vietti TJ, Strother DR, Ragab AH, Pratt CB (1993) Phase I trial of paclitaxel in children with refractory solid tumors: a Pediatric Oncology Group study. J Clin Oncol 11: 2324
12. Kumar GN, Walle UK, Walle T (1994) Cytochrome P450 3A-mediated human liver microsomal taxol 6α-hydroxylation. J Pharmacol Exp Ther 268: 1160
13. Longnecker SM, Donehower RC, Cates AE, Chen T-L, Brundrett RB, Grochow LB, Ettinger DS, Colvin M (1987) High-performance liquid chromatographic assay for taxol in human plasma and urine and pharmacokinetics in a phase I trial. Cancer Treat Rep 71: 53
14. Ohtsu T, Sasaki Y, Tamura T, Miyata Y, Nakanomyo H, Nishiwaki Y, Saijo N (1995) Clinical pharmacokinetics and pharmacodynamics of paclitaxel: a 3-hour infusion versus a 24-hour infusion. Clin Cancer Res 1: 599
15. 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

16. Rowinsky EK, Burke PJ, Karp JE, Tucker RW, Ettinger DS, Donehower RC (1989) Phase I and pharmacodynamic study of taxol in refractory acute leukemias. Cancer Res 49: 4640
17. Rowinsky EK, Gilbert MR, McGuire WP, Noe DA, Grochow LB, Forastiere AA, Ettinger DS, Lubejko BG, Clark B, Sartorius SE, Cornblath DR, Hendricks CB, Donehower RC (1991) Sequences of taxol and cisplatin: a phase I and pharmacologic study. J Clin Oncol 9: 1692
18. Roy SN, Horwitz SB (1985) A phosphoglycoprotein associated with taxol resistance in J774.2 cells. Cancer Res 45: 3856
19. Schilder LE, Egorin MJ, Zuhowski EG, Rossof AH (1994) The pharmacokinetics of taxol in a dialysis patient. Proc Annu Meet Am Soc Clin Oncol 13: 136, abstract 338
20. Schiller JH, Storer B, Tutsch K, Arzoomanian R, Alberti D, Feierabend C, Spriggs D (1994) Phase I trial of 3-hour infusion of paclitaxel with or without granulocyte colony-stimulating factor in patients with advanced cancer. J Clin Oncol 12: 241
21. 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
22. Sonnichsen DS, Liu Q, Schuetz EG, Schuetz JD, Pappo A, Relling MV (1995) Variability in human cytochrome P450 paclitaxel metabolism. J Pharmacol Exp Ther 275: 566
23. Wiernik PH, Schwartz EL, Strauman JJ, Dutcher JP, Lipton RB, Paietta E (1987) Phase I clinical and pharmacokinetic study of taxol. Cancer Res 47: 2486
24. Wiernik PH, Schwartz EL, Einzig A, Strauman JJ, Lipton RB, Dutcher JP (1987) Phase I trial of taxol given as a 24-hour infusion every 21 days: responses observed in metastatic melanoma. J Clin Oncol 5: 1232