Anti-Cancer Drugs 2000, **11,** pp. 813–820

Clinical report

Metabolism and excretion of paclitaxel after oral administration in combination with cyclosporin A and after i.v. administration

Mirte M Malingré,[1,2] Jan HM Schellens,[1,3] Olaf van Tellingen,[1] Hilde Rosing,[2] Franciska J Koopman,[2] Ken Duchin,[4] Wim W ten Bokkel Huinink,[1] Martha Swart[1] and Jos H Beijnen[1–3]

[1]Department of Medical Oncology, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands. [2]Department of Pharmacy and Pharmacology, The Netherlands Cancer Institute/Slotervaart Hospital, Louwesweg 6, 1066 EC Amsterdam, The Netherlands. [3]Division of Drug Toxicology, Faculty of Pharmacy, Utrecht University, Sorbonnelaan 16, 3584 CA Utrecht, The Netherlands. [4]Baker Norton Pharmaceuticals, 4400 Biscayne Boulevard, Miami, FL 33137, USA

The objective of this study was to compare the quantitative excretion of paclitaxel and metabolites after i.v. and oral drug administration. Four patients received 300 mg/m^2 paclitaxel orally 30 min after 15 mg/kg oral cyclosporin A, co-administered to enhance the uptake of paclitaxel. Three weeks later these and three other patients received 175 mg/m^2 paclitaxel by i.v. infusion. Blood samples, urine and feces were collected up to 48–96 h after administration, and analyzed for paclitaxel and metabolites. The area under the plasma concentration–time curve of paclitaxel after i.v. administration (175 mg/m^2) was 16.2 $\pm$ 1.7 μM · h and after oral administration (300 mg/m^2) 3.8 $\pm$ 1.5 μM · h. Following i.v. infusion of paclitaxel, total fecal excretion was 56 $\pm$ 25%, with the metabolite 6α-hydroxypaclitaxel being the main excretory product (37 $\pm$ 18%). After oral administration of paclitaxel, total fecal excretion was 76 $\pm$ 21%, of which paclitaxel accounted for 61 $\pm$ 14%. In conclusion, after i.v. administration of paclitaxel, excretion occurs mainly in the feces with the metabolites as the major excretory products. Orally administered paclitaxel is also mainly excreted in feces but with the parent drug in highest amounts. We assume that this high amount of parent drug is due to incomplete absorption of orally administered paclitaxel from the gastrointestinal tract. [© 2000 Lippincott Williams & Wilkins.]

Key words: Excretion, metabolism, oral administration, paclitaxel.

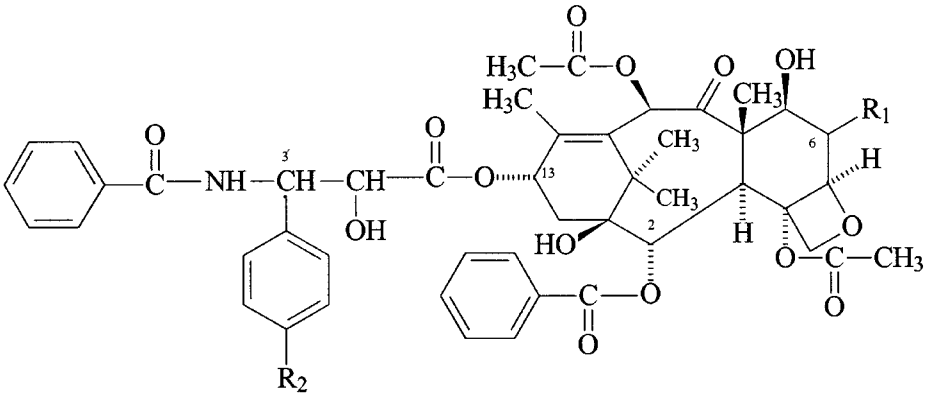
This work was supported by the Dutch Cancer Society grant NKI 98-1799.

Correspondence to MM Malingré, Department of Pharmacy and Pharmacology, The Netherlands Cancer Institute/Slotervaart Hospital, Louwesweg 6, 1066 EC Amsterdam, The Netherlands.
Tel: (+31) 20 512 4657; Fax: (+31) 20 512 4753;
E-mail: apmmg@slz.nl

Introduction

Paclitaxel is a potent anticancer drug with proven activity against a number of human solid tumors and has become standard treatment as a single agent or in combination chemotherapy for the management of advanced breast, ovarian and non-small cell lung cancer.[1,2] The drug is currently administered i.v. at different dosages and time schedules, and optimization of the clinical application is pursued. Elimination studies in man have shown that the primary route of elimination of i.v. administered paclitaxel occurs via hepatic metabolism and biliary excretion, whereas renal excretion is minimal.[3,4] In man, three major metabolic products of paclitaxel have been detected, i.e. 6α-hydroxypaclitaxel, 3′*p*-hydroxypaclitaxel and 6α,3′*p*-dihydroxypaclitaxel (Figure 1).[3,5,6] The metabolite 6α-hydroxypaclitaxel is in general the principal metabolite. *In vitro* cytotoxicity studies have shown that all three metabolites are substantially less active than paclitaxel.[5–7] Biotransformation of paclitaxel is catalyzed by two cytochrome P450 (CYP) isoenzymes. The formation of 6α-hydroxypaclitaxel is catalyzed by CYP 2C8, whereas the metabolite 3′*p*-hydroxypaclitaxel is formed by CYP 3A4.[8–10] The dihydroxylated metabolite 6α,3′*p*-dihydroxypaclitaxel results from stepwise hydroxylations by CYPs 2C8 and 3A4 (Figure 2).[8,9]

Recently, we reported on the oral administration of paclitaxel. Development of treatment of paclitaxel by the oral route has been limited due to its low oral bioavailability (below 10%). Preclinical studies at our



Structure	R_1	R_2
Paclitaxel	H	H
6α-hydroxypaclitaxel	OH	H
3′*p*-hydroxypaclitaxel	H	OH
6α,3′*p*-dihydroxypaclitaxel	OH	OH

Figure 1. Molecular structures of paclitaxel, 6α-hydroxypaclitaxel, 3′*p*-hydroxypaclitaxel and 6α,3′*p*-dihydroxypaclitaxel.

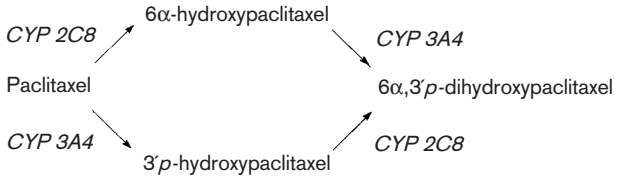


Figure 2. Major metabolic pathways of paclitaxel.

Institute have shown that the low oral bioavailability of paclitaxel is, at least in part, due to paclitaxel's affinity for the multidrug efflux pump P-glycoprotein (P-gp), which is abundantly present in the gastro-intestinal tract. In *mdr1a* P-gp knockout mice, which lack functional P-gp activity in the gut, bioavailability of orally administered paclitaxel was increased up to 35%.[11] Because uptake of orally administered paclitaxel was complete, as was shown by the negligible amount of paclitaxel excreted in feces, it can be concluded that first-pass metabolism is an important factor in the low oral bioavailability of paclitaxel as well. Additional studies in wild-type mice revealed a pronounced increase in the oral bioavailability of paclitaxel when the drug was combined with cyclosporin A (CsA), an efficacious blocker of P-gp and substrate/inhibitor for the CYP 3A4 metabolic enzymes.[12] Based on our preclinical studies we recently initiated a clinical proof of concept study of orally administered paclitaxel (60 mg/m^2) in combination with oral CsA (15 mg/kg). Co-administration of CsA resulted in a pronounced increase in the systemic exposure of orally administered paclitaxel and oral bioavailability of the drug increased from 4% for paclitaxel administered as a single agent up to 47% when the drug was combined with CsA.[13,14] The increase in systemic exposure by CsA was most likely caused by inhibition of P-gp and, in addition, by inhibition of paclitaxel metabolism, as we observed altered paclitaxel metabolism following CsA administration.[14] Furthermore, CsA may have other unknown effects that may influence paclitaxel absorption.

In order to further increase the systemic exposure to orally administered paclitaxel we investigated dose escalation of oral paclitaxel in combination with CsA.[15] At the maximum tolerated dose of 300 mg/m^2 oral paclitaxel, we studied the quantitative excretion of the drug and compared this with the quantitative excretion of i.v. administered paclitaxel.

Patients and methods

Patient population

Patients with a histologically confirmed cancer refractory to current therapies were eligible for the study. Previous radiotherapy or chemotherapy other than

taxoid therapy was allowed, provided that the last treatment was at least 4 weeks prior to study entry and any resulting toxicities were resolved. Eligibility criteria included acceptable bone marrow function (white blood cells $>3.0\times10^9$/l; platelets $>100\times10^9$/l), liver function (serum bilirubin $\leqslant25$ μmol/l; serum albumin $\geqslant25$ g/l), kidney function (serum creatinine $\leqslant160$ μmol/l or clearance $\geqslant50$ ml/min) and a WHO performance status $\leqslant2$. Patients were not eligible if they suffered from uncontrolled infectious disease, neurologic disease, bowel obstruction or symptomatic brain metastases. Other exclusion criteria were concomitant use of known P-gp inhibitors and chronic use of H_2-receptor antagonists or proton pump inhibitors. The study protocol was approved by the Medical Ethics Committee of the Institute and all patients gave written informed consent.

Dosage and administration

Patients received 300 mg/m^2 paclitaxel orally 30 min after the oral administration of 15 mg/kg CsA. Three weeks later these patients received 175 mg/m^2 paclitaxel by a 3-h i.v. infusion. Patients continued on a 3-weekly schedule of i.v. paclitaxel, if this was considered in their best interest. The i.v. formulation of paclitaxel (Paxene®, paclitaxel 6 mg/ml, dissolved in Cremophor EL and ethanol 1:1 w/v; Baker Norton Pharmaceuticals, Miami, FL) was used for both i.v. and oral administration of paclitaxel. CsA was administered as capsules (Neoral®; Novartis, Basel, Switzerland). To prevent hypersensitivity reactions patients were premedicated with dexamethasone 20 mg orally 12 and 6 h prior to, clemastine 2 mg i.v. and cimetidine 300 mg i.v. 30 min prior to both i.v. and oral paclitaxel administration. To prevent nausea and vomiting patients received 1 mg oral granisetron (Kytril®) prior to oral paclitaxel administration. In addition, two patients received a light breakfast at least 2 h prior to oral drug administration. Intake of food was not allowed until 2 h following oral administration of paclitaxel.

Sample collection

Blood samples for pharmacokinetic analyses were collected during course 1 and 2. Following oral administration samples were obtained pre-dosing, at 15, 30, 45, 60, 75 and 90 min, and 2, 3, 4, 7, 10, 24, 30 and 48 h after paclitaxel ingestion. For i.v. administered paclitaxel, a previously established limited sampling model using two timed blood samples drawn at 1 and 8 h post-infusion was used.[16] Blood samples were collected in heparinized tubes. For the analysis of paclitaxel and metabolites, blood samples were centrifuged, and plasma was separated and immediately stored at -20°C until analysis. For CsA analysis, 1 ml of whole blood was transferred and stored at 4°C until analysis. Urine was collected from 0 to 24 h and 24 to 48 h after paclitaxel administration. Samples were stabilized with a mixture of 5% Cremophor EL/ethanol 1:1 v/v to prevent paclitaxel precipitation and these samples were stored at -20°C. The stools were collected in separate portions up to 4 days after dosing. The fecal samples were homogenized in 10 parts of water with a maximum of 2000 ml and aliquots of the suspension were stored at -20°C.

Sample analysis

Paclitaxel and metabolite concentrations in plasma, urine and feces were determined using validated high-performance liquid chromatography (HPLC) assays.[17,18,11] All assays used 2′-methylpaclitaxel as the internal standard. Pretreatment of the plasma samples involved solid-phase extraction (SPE) on Cyano Bond Elut columns. The concentrations of the plasma metabolic products 6α-hydroxypaclitaxel, 3′*p*-hydroxypaclitaxel and 6α,3′*p*-dihydroxypaclitaxel were determined using the paclitaxel standard curve with a correction of 1.14 for the metabolite 6α,3′*p*-dihydroxypaclitaxel.[17] Pretreatment of urine samples involved liquid–liquid extraction (LLE) with *n*-butylchloride.[18] Fecal samples were pretreated by LLE with diethyl ether followed by automated SPE using Cyano Bond Elut columns. Analysis of the fecal samples was analogous to the assay used by Sparreboom *et al.*[11] with minor modifications to make the assay more suitable for human feces. Further details and validation of the assay will be published elsewhere. The lower limit of quantitation for paclitaxel and metabolites was 10 ng/ml for plasma, 25 ng/ml for urine and 250 ng/ml for feces. CsA whole blood concentrations were analyzed using a specific fluorescence polarization immunoassay (FPIA, TDxFLx; Abbott Laboratories, Amstelveen, The Netherlands).[19] The concentration of Cremophor EL in feces was measured after oral intake of paclitaxel using a validated HPLC assay[20] with minor modifications.[21]

Pharmacokinetic analysis

Non-compartmental pharmacokinetic methods were applied to process the results.[22] The maximal drug concentration (C_{max}) and time to maximal drug concentration (T_{max}) were obtained directly from the experimental data. The area under the concentration–time curve (AUC) was calculated by the trapezoidal

rule up to the last measured time point with extrapolation to infinity using the terminal rate constant k. The time above the threshold concentration of 0.1 μM ($T > 0.1$ μM) was determined using linear interpolation. The excretion of paclitaxel, metabolites and Cremophor EL in feces and urine was calculated relative to the administered dose. Renal clearance of paclitaxel (Cl_r) was calculated by dividing the amount of drug excreted in the urine by the plasma AUC. A statistical analysis of the data was performed using the Pearson correlation coefficient. The *a priori* level of significance was $p = 0.05$.

Results

Patients and treatment

Seven patients (four males and three females) were enrolled in the study. At study entry, the median age was 55 years (range 35–78) and the median performance score was 1 (range 0–2). Primary tumor types included breast ($n = 1$), esophagus ($n = 1$), thymoma ($n = 1$), gall bladder carcinoma ($n = 1$) and adenocarcinoma of unknown primary site ($n = 3$). All patients had received prior surgical therapy, radiotherapy and/or chemotherapy. Four patients received both oral and i.v. administered paclitaxel; three other patients received only i.v. administered paclitaxel.

Pharmacokinetics

Cumulative excretion profiles of paclitaxel and metabolites after i.v. and oral administration of paclitaxel are depicted in Figure 3(a and b).

After both i.v. and oral administration, excretion of paclitaxel and metabolites occurred mainly in the feces, i.e. 56% ($n = 7$) and 76% ($n = 4$), respectively (Tables 1–3). In most of the patients (i.v. $n = 5$ and oral $n = 4$) more than 75% of the total fecal excretion was recovered within 2 days following administration. After i.v. administration, the main compound recovered in the feces was the metabolite 6α-hydroxypaclitaxel, accounting for 37% of the administered dose. After oral administration, paclitaxel was mainly excreted as unchanged drug accounting for 61% of the administered dose. The amount of Cremophor EL recovered in feces after oral intake of paclitaxel was 32% of the administered Cremophor EL dose. The total fraction of Cremophor EL excreted in feces for each patient was significantly correlated with the total fraction of paclitaxel excreted in feces ($p = 0.04$, $r = 0.96$).

Urinary excretion of paclitaxel after both i.v. and oral administration was minimal, i.e. 9% ($n = 6$) and 1% ($n = 4$) of the administered dose, respectively (Tables 1–3). Renal clearance (Cl_r) of paclitaxel was 1.1 ± 0.4 l/h/m^2 after i.v. administration and 1.1 ± 0.6 l/h/m^2 after oral drug intake. More than 80% of the total urinary excretion of paclitaxel after i.v. and oral administration occurred within 1 day. In urine samples no metabolites of paclitaxel could be detected.

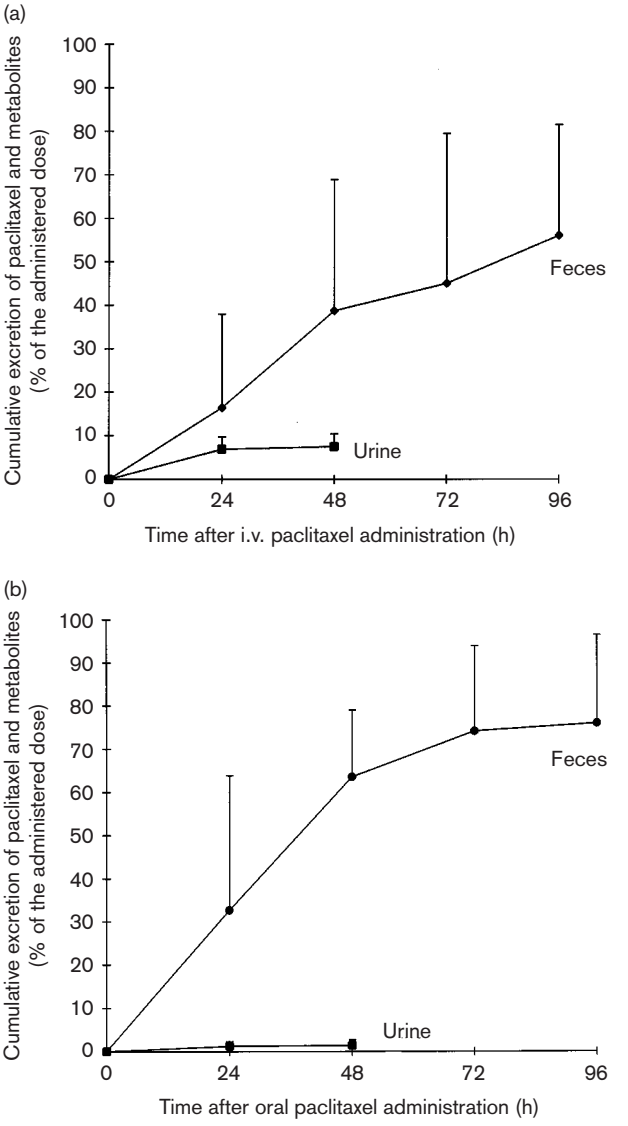


Figure 3. (a) Cumulative urinary and fecal excretion of paclitaxel and metabolites after i.v. administration of paclitaxel (175 mg/m^2 as a 3-h infusion) in seven patients. (b) Cumulative urinary and fecal excretion of paclitaxel and metabolites after oral administration of paclitaxel (300 mg/m^2) in four patients.

Using our limited sampling model the calculated plasma AUC after i.v. administration of 175 mg/m^2 given by a 3-h infusion was 16.2 ± 1.7 μM · h. After oral administration of 300 mg/m^2 paclitaxel in combination with 15 mg/kg CsA, the plasma AUC was

Table 1. Urinary and fecal excretion values of paclitaxel and metabolites after i.v. administration of pacitaxel (175 mg/m^2 i.v.) ($n=7$)

Patient	Urine	Feces			
	Paclitaxel (% of dose)	Paclitaxel (% of dose)	6α-HP (% of dose)	3′*p*-HP (% of dose)	6α,3′*p*-DHP (% of dose)
1	11.0	5.8	22.7	6.0	4.8
2	ND	8.7	33.7	5.4	4.7
3	9.0	11.8	41.6	4.2	5.3
4	13.5	3.4	9.5	1.3	1.8
5	7.5	13.6	62.8	4.4	6.2
6	6.4	13.5	51.3	8.4	12.1
7	3.4	8.4	36.5	3.5	2.2
Mean ± SD	8.5 ± 3.5	9.3 ± 3.9	36.9 ± 17.6	4.7 ± 2.2	5.3 ± 3.4

6α-HP, 6α-hydroxpaclitaxel; 3′*p*-HP, 3′*p*-hydroxpaclitaxel; 6α,3′*p*-DHP, 6α,3′*p*-dihydroxypaclitaxel. ND, not determined due to loss of urine.

Table 2. Urinary and fecal excretion values of paclitaxel and metabolites and the co-solvent Cremophor EL after oral administration of pacitaxel (300 mg/m^2) ($n=4$)

Patient	Urine	Feces				
	Paclitaxel (% of dose)	Paclitaxel (% of dose)	6α-HP (% of dose)	3′*p*-HP (% of dose)	6α,3′*p*-DHP (% of dose)	Cremophor EL (% of dose)
1	3.4	54.1	12.7	3.7	3.5	31.0
2	0.4	68.0	5.5	1.0	0.7	33.8
3	0.8	76.0	18.9	3.2	4.3	39.8
4	1.1	45.6	5.0	0.6	1.0	23.1
Mean ± SD	1.4 ± 1.3	60.9 ± 13.6	10.5 ± 6.6	2.1 ± 1.6	2.4 ± 1.8	31.9 ± 6.9

6α-HP, 6α-hydroxpaclitaxel; 3′*p*-HP, 3′*p*-hydroxpaclitaxel; 6α,3′*p*-DHP, 6α,3′*p*-dihydroxypaclitaxel.

Table 3. Urinary and fecal excretion values of paclitaxel and metabolites following oral and i.v. administration of paclitaxel (mean ± SD)

	Oral 300 mg/m^2 ($n=4$)	i.v. 175 mg/m^2 ($n=7$)
Urine (% of dose)		
paclitaxel	1.4 ± 1.3	8.5 ± 3.5
Feces (% of dose)		
paclitaxel	60.9 ± 13.6	9.3 ± 3.9
6α-HP	10.5 ± 6.6	36.9 ± 17.6
3′*p*-HP	2.1 ± 1.6	4.7 ± 2.2
6α,3′*p*-DHP	2.4 ± 1.8	5.3 ± 3.4
total	76.0 ± 20.6	56.2 ± 25.1

6α-HP, 6α-hydroxpaclitaxel; 3′*p*-HP, 3′*p*-hydroxpaclitaxel; 6α,3′*p*-DHP, 6α,3′*p*-dihydroxypaclitaxel.

3.8 ± 1.5 μM·h (Table 4). For i.v. administered paclitaxel we could not determine pharmacokinetic parameters of the metabolites due to the fact that only two timed blood samples were drawn. For orally administered paclitaxel, plasma AUC(t) values of the metabolites 6α-hydroxypaclitaxel, 3′*p*-hydroxypaclitaxel and 6α,3′*p*-dihydroxypaclitaxel were 1.5 ± 1.5, 1.0 ± 0.8 and 0.8 ± 0.8 μM · h, respectively. AUC(t) values have been calculated because extrapolation of the AUC could not be performed properly due to the limited detection time of the metabolites. Mean CsA whole blood pharmacokinetic parameters were: C_{max}=1.9 ± 0.4 mg/l, AUC=18.8 ± 2.7 mg · h/l and T_{max} = 2.4 ± 1.5 h (n = 4).

Discussion

Following i.v. administration of paclitaxel the major excretion route of paclitaxel and metabolites was feces, i.e. 56% of the administered dose. The major compounds detected in feces were the metabolites, i.e. 47% of the administered dose, of which 6α-hydroxypaclitaxel accounted for 37%. Extensive excretion of metabolites in feces supports the hypothesis that paclitaxel metabolism, especially biotransformation to 6α-hydroxypaclitaxel, followed by biliary excretion comprises an important elimination route of i.v. administered paclitaxel. Our results are in good agreement with those obtained by Walle *et al.*[4] who

Table 4. Plasma pharmacokinetic parameters of paclitaxel and metabolites after i.v. (175 mg/m^2) and oral administration (300 mg/m^2) (mean ± SD)

		Paclitaxel	6α-Hydroxypaclitaxel	3′*p*-Hydroxypaclitaxel	6α,3′*p*-Hydroxypaclitaxel
i.v. ($n=6$)[a]	AUC (μM · h)	16.2 ± 1.7	ND	ND	ND
	$T>0.1$ μM (h)	22.3 ± 2.8	ND	ND	ND
Oral ($n=4$)	AUC (μM · h)	3.8 ± 1.5	1.5 ± 1.5[b]	1.0 ± 0.8[b]	0.8 ± 0.8[b]
	$T>0.1$ μM (h)	9.3 ± 4.7	ND	ND	ND
	C_{max} (μM)	0.36 ± 0.17	0.15 ± 0.12	0.09 ± 0.05	0.08 ± 0.07
	T_{max} (h)	3.8 ± 0.5	5.2 ± 2.0	6.0 ± 2.0	7.0 ± 0.1

ND, not determined.
[a]One patient was not evaluable because one sample of the limited sampling model was not taken.
[b]AUC(t) values.

treated patients with radiolabeled paclitaxel (Taxol®) and extracted 59% of the administered radioactivity from feces of which 5% consisted of paclitaxel and 26% of the metabolite 6α-hydroxypaclitaxel. In that study total radioactivity recovered in feces amounted up to 71%. Our preclinical studies in mice treated with i.v. administered paclitaxel also showed that a substantial fraction of the administered dose (26%) was excreted in feces as metabolites; however, the excretion of unchanged paclitaxel of 51% in feces was substantially higher than in humans.[23] Thus, although paclitaxel metabolism in mice qualitatively resembles that in humans, the drug is less extensively metabolized in mice than in humans.

Following oral paclitaxel administration in combination with the P-gp inhibitor CsA the major excretion route of paclitaxel and metabolites was also with feces, i.e. 76% of the administered dose. The major compound recovered in feces was paclitaxel, accounting for 61% of the administered dose. In our preclinical studies with oral paclitaxel in both wild-type and *mdr1a* P-gp knockout mice we observed that the fecal excretion of paclitaxel decreased from 87% in wild-type mice to 2% in the *mdr1a* P-gp knock-out mice.[11] This large decrease in fecal excretion of paclitaxel suggests almost complete (re)uptake of the drug from the gastrointestinal tract in P-gp knockout mice. Thus, according to our preclinical studies we expected only a small fraction of the paclitaxel dose excreted in the feces instead of the observed 61%. We assume that the large amount of paclitaxel recovered in feces in our study is largely due to excretion of unabsorbed drug, which is supported by the lower plasma AUC value of orally administered paclitaxel (300 mg/m^2) compared to i.v. administered paclitaxel (175 mg/m^2), i.e. 3.8 and 16.2 μM · h, respectively. The plasma pharmacokinetic data of oral paclitaxel in the dose-escalation study,[15] of which this excretion study was part, revealed significant increases in the paclitaxel AUC values when the dose was escalated; however, the increases in systemic exposure were disproportional with the increases in dose, suggesting incomplete absorption of the drug, which was more pronounced at the higher dose levels. In that study, we suggested that the incomplete absorption of orally administered paclitaxel was most likely caused by the poor aqueous solubility of paclitaxel in the gastrointestinal tract. A second potential explanation we proposed was incomplete blockade of intestinal P-gp by CsA. Incomplete P-gp inhibition by CsA would necessitate the use of more potent P-gp modulators such as PSC 833.[24,25] In this study, we propose a third possibility, i.e. entrapment of paclitaxel by Cremophor EL in the gastrointestinal tract which will hamper its release and may therefore lead to incomplete absorption. This hypothesis is supported by the large amounts of Cremophor EL that we detected in feces after oral intake of paclitaxel, i.e. 32% of the administered Cremophor EL dose, which are in contrast to the undetectable Cremophor EL levels in feces of the *mdr1a* P-gp knockout mice after oral paclitaxel administration (unpublished data). Moreover, the total fraction of Cremophor EL excreted in feces for each patient was significantly correlated with the total fraction of paclitaxel excreted in feces ($p=0.04$, $r=0.96$). Further research is warranted to get a better picture of the incomplete absorption of paclitaxel after oral ingestion. We are currently investigating the absorption of oral paclitaxel administered in a formulation without Cremophor EL.

Urinary excretion of paclitaxel was low after both i.v. and oral administration, and accounted for 9 and 1% of the administered dose, respectively. Clearly, urinary excretion contributes minimally to the excretion of paclitaxel as was shown in previous studies.[3,4] The lower urinary excretion fraction of paclitaxel after oral drug administration compared to i.v. administration can be explained by the incomplete absorption of orally administered paclitaxel. In addition, CsA may inhibit urinary paclitaxel excretion and may therefore contribute to the lower amount of the dose recovered in urine following oral administration. Lum *et al.*[26]

found a 40% decrease in renal clearance of i.v. administered etoposide in combination with CsA compared to etoposide alone, which was presumed to be caused by inhibition of P-gp-mediated drug transport in the kidneys. However, in this study, renal clearance of paclitaxel after i.v. and oral administration was comparable, suggesting that either P-gp is not a major factor in urinary excretion of paclitaxel or that P-gp in the renal tubule is not inhibited by CsA given at the current dose level.

The total urinary and fecal excretion of paclitaxel and the three metabolites 6α-hydroxypaclitaxel, 3′*p*-hydroxypaclitaxel and 6α,3′*p*-dihydroxypaclitaxel amounts to 65 and 77% of the administered i.v. and oral paclitaxel dose, respectively. One patient in this study (patient 4) suffered from obstipation, which resulted in incomplete feces collection following both i.v. and orally administered paclitaxel. If this patient is omitted, total recovery in the remaining patients becomes 71 and 86% of the administered i.v. and oral dose, respectively. Thus, in our study the majority of parent drug and metabolites after both i.v. and oral paclitaxel administration was recovered. The remaining unrecovered fraction of the administered dose may be lost due to incomplete urine and feces collection and/or metabolism to yet unidentified metabolites. Monsarrat *et al*.[3] detected five metabolites in human bile and Huizing *et al*.[27] found 11 putative metabolites of paclitaxel in human plasma.

In conclusion, paclitaxel given by i.v. infusion is mainly excreted in the feces with the hydroxylated metabolites as the major excretory products. Orally administered paclitaxel is also mainly excreted in the feces, but with the parent drug in highest amounts. We assume that the high amount of parent drug recovered in feces after oral administration is due to incomplete absorption from the gastrointestinal tract, which may be due to paclitaxel's poor aqueous solubility, incomplete P-gp inhibition by CsA, entrapment of paclitaxel by Cremophor EL and/or other, yet unknown, factors.

References

1. Rowinsky EK, Donehower RC. Paclitaxel (Taxol). *N Engl J Med* 1995; **332**: 1004–14.
2. Natale RB. Experience with new chemotherapeutic agents in non-small cell lung cancer. *Chest* 1998; **113**(suppl 1): 32–9.
3. Monsarrat B, Alvinerie P, Wright M, *et al*. Hepatic metabolism and biliary excretion of Taxol in rats and humans. *J Natl Cancer Inst Monogr* 1993; **15**: 39–46.
4. Walle T, Walle UK, Kumar GN, Bhalla KN. Taxol metabolism and disposition in cancer patients. *Drug Metab Disp* 1995; **23**: 506–12.
5. Harris JW, Katki A, Anderson LW, Chmurny GN, Paukstelis JV, Collins JM. Isolation, structural determination, and biological activity of 6 alpha-hydroxytaxol, the principal human metabolite of taxol. *J Med Chem* 1994; **37**: 706–9.
6. Sparreboom A, Huizing MT, Boesen JJB, Nooijen WJ, Van Tellingen O, Beijnen JH. Isolation, purification and biological activity of mono-and dihydroxylated paclitaxel (Taxol) metabolites from human faeces. *Cancer Chemother Pharmacol* 1995; **36**: 299–304.
7. Kumar GN, Ray S, Walle T, *et al*. Comparative *in vitro* cytotoxic effects of taxol and its major human metabolite 6α-hydroxytaxol. *Cancer Chemother Pharmacol* 1995; **36**: 129–35.
8. Harris JW, Rahman A, Kim BR, Guengerich FP, Collins JM. Metabolism of Taxol by human hepatic microsomes and liver slices: participation of cytochrome P450 3A4 and an unknown P450 enzyme. *Cancer Res* 1994; **54**: 4026–35.
9. Cresteil T, Monsarrat B, Alvinerie P, Treluyer JM, Vieira I, Wright M. Taxol metabolism by human liver microsomes: identification of cytochrome P450 isozymes involved in its biotransformation. *Cancer Res* 1994; **54**: 386–92.
10. Rahman A, Korzekwa KR, Grogan J, Gonzalez FJ, Harris JW. Selective biotransformation of taxol to 6 alpha-hydroxytaxol by human cytochrome P450 2C8. *Cancer Res* 1994; **54**: 5543–6.
11. Sparreboom A, Van Asperen J, Mayer U, *et al*. Limited oral bioavailability and active epithelial excretion of paclitaxel (Taxol) caused by P-glycoprotein in the intestine. *Proc Natl Acad Sci USA* 1997; **94**: 2031–5.
12. Van Asperen J, Van Tellingen O, Van der Valk MA, Rozenhart M, Beijnen JH. Enhanced oral absorption and decreased elimination of paclitaxel in mice cotreated with cyclosporin A. *Clin Cancer Res* 1998; **4**: 2293–97.
13. Meerum Terwogt JM, Beijnen JH, ten Bokkel Huinink WW, Rosing H, Schellens JHM. Co-administration of cyclosporin enables oral therapy with paclitaxel. *Lancet* 1998; **352**: 285.
14. Meerum Terwogt JM, Malingré MM, Beijnen JH, *et al*. Co-administration of cyclosporin enables oral therapy with paclitaxel. *Clin Cancer Res* 1999; **5**: 3379–84.
15. Malingré MM, Meerum Terwogt JM, Beijnen JH, *et al*. Phase I and pharmacokinetic study of oral paclitaxel. *J Clin Oncol* 2000; **18**: 2468–75.
16. Huizing MT, Van Warmerdam LJC, Rosing H, *et al*. Limited sampling strategies for investigating paclitaxel pharmacokinetics in patients receiving 175 mg/m^2 as a 3-hour infusion. *Clin Drug Invest* 1995; **9**: 344–53.
17. Huizing MT, Sparreboom A, Rosing H, Van Tellingen O, Pinedo HM, Beijnen JH. Quantification of paclitaxel metabolites in human plasma by high-performance liquid chromatography. *J Chromatogr B* 1995; **674**: 261–8.
18. Huizing MT, Rosing H, Koopman FJ, Keung ACF, Pinedo HM, Beijnen JH. High-performance liquid chromatographic procedures for the quantitative determination of paclitaxel (Taxol) in human urine. *J Chromatogr B* 1995; **664**: 373–82.
19. Chan GL, Weinstein SS, Lefor WW, Spoto E, Kahana L, Shires DL. Relative performance of specific and non-specific fluorescence immunoassay for cyclosporin in transplant patients. *Ther Drug Monit* 1992; **14**: 42–7.

20. Sparreboom A, van Tellingen O, Huizing MT, Nooijen WJ, Beijnen JH. Determination of Polyoxyethyleneglycerol Triricinoleate 35 (Cremophor EL) in plasma by pre-column derivatization and reversed-phase high-performance liquid chromatography. *J Chromatogr B* 1996; **681**: 355–62.
21. van Tellingen O, Huizing MT, Nannan Panday VR, Schellens JHM, Nooijen WJ, Beijnen JH. Cremophor EL causes (pseudo) nonlinear pharmacokinetics of paclitaxel in patients. *Br J Cancer* 1999; **81**: 330–5.
22. Gibaldi M, Perrier D. Noncompartmental analysis based on statistical moment theory. In: Swarbrick J, ed. *Pharmacokinetics*. New York: Marcel Dekker 1992: 409–17.
23. Sparreboom A, Van Tellingen O, Nooijen WJ, Beijnen JH. Tissue distribution, metabolism and excretion of paclitaxel in mice. *Anti-Cancer Drugs* 1996; **7**: 78–86.
24. Sikic BI, Fisher GA, Lum BL, Halsey J, Beketic-Oreskovic L, Chen G. Modulation and prevention of multidrug resistance by inhibitors of P-glycoprotein. *Cancer Chemother Pharmacol* 1997; **36**: 451–8.
25. van Asperen J, van Tellingen O, Sparreboom A, *et al*. Enhanced oral bioavailability of paclitaxel in mice co-treated with the P-glycoprotein blocker SDZ PSC 833. *Br J Cancer* 1997; **76**: 1181–3.
26. Lum BL, Kaubisch S, Yahanda AM, *et al*. Alteration of etoposide pharmacokinetics and pharmacodynamics by cyclosporin in a phase I trial to modulate multidrug resistance. *J Clin Oncol* 1992; **10**: 1635–42.
27. Huizing MT, Keung ACF, Rosing H, *et al*. Pharmacokinetics of paclitaxel and metabolites in a randomized comparative study in platinum-pretreated ovarian cancer patients. *J Clin Oncol* 1993; **11**: 2117–35.

(Received 8 August 2000; accepted 18 August 2000)