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ORIGINAL ARTICLE

Novel paclitaxel formulations for oral application: a phase I pharmacokinetic study in patients with solid tumours

S. A. Veltkamp · H. Rosing · A. D. R. Huitema · M. R. Fetell · A. Nol · J. H. Beijnen · J. H. M. Schellens

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Abstract
Purpose To explore the pharmacokinetics (PKs) of paclitaxel and two major metabolites after three single oral administrations of a novel drinking solution and two capsule formulations in combination with cyclosporin A (CsA) in patients with advanced cancer. Moreover, the tolerability and safety of the formulations was studied. In addition, single nucleotide polymorphisms in the multidrug resistance (*MDR1*) gene were determined.
Patients and methods Ten patients were enrolled and randomized to receive CsA 10 mg/kg followed by oral paclitaxel 180 mg given as (1) drinking solution (formulation 1), (2) capsule formulation 2B, and (3) capsule formulation 2C on day 1, 8, or 15.
Results The median C_{max} of paclitaxel was 0.42 (0.23–0.96), 0.48 (0.08–0.59), and 0.39 (0.11–1.03) μg/ml and the area under the plasma concentration–time curve was 2.83 (1.69–5.12), 2.01 (1.57–3.04), and 2.67 (1.05–3.61) μg h/ml following administration of formulations 1, 2B, and 2C, respectively. The novel formulations were tolerated after single oral dose without causing relevant gastrointestinal or haematological toxicity.
Conclusions The PK and metabolism of paclitaxel were comparable between the oral formulations co-administered with CsA.

Keywords Phase I · Pharmacokinetics · Paclitaxel · Cremophor-free · Oral administration

S. A. Veltkamp · J. H. M. Schellens
Division of Experimental Therapy, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 Amsterdam, The Netherlands

S. A. Veltkamp (✉) · A. Nol · J. H. Beijnen · J. H. M. Schellens
Department of Medical Oncology, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 Amsterdam, The Netherlands
e-mail: s.veltkamp@nki.nl

H. Rosing · A. D. R. Huitema · J. H. Beijnen
Department of Pharmacy and Pharmacology, The Netherlands Cancer Institute/Slotervaart Hospital, 1066 Amsterdam, The Netherlands

J. H. Beijnen · J. H. M. Schellens
Division of Biomedical Analysis, Faculty of Pharmaceutical Sciences, University of Utrecht, 3584 Utrecht, The Netherlands

M. R. Fetell
Ivax Research, Inc., 4400 Biscayne Boulevard, Miami, FL 33137, USA

Introduction

Currently, paclitaxel is only marketed as an intravenous (i.v.) formulation. Paclitaxel is poorly soluble in most pharmaceutical solvents. Therefore, it is formulated in the marketed i.v. formulation in a 1:1 combination of the solubilizing agent polyoxyethylated castor oil [Cremophor® EL (CrEL)] and dehydrated ethanol. CrEL has been reported to be responsible for severe hypersensitivity reactions [32] and the non-linear pharmacokinetic (PK) behaviour of i.v. administered paclitaxel [22, 27, 28].

Oral administration of paclitaxel is attractive because it may enable the development of treatment regimens resulting in plasma concentrations at a pharmacologically relevant level for more prolonged periods of time. Moreover, oral administration is more

Table 1 Composition of the oral formulations

Formulation 1[a]	% (w/v)	Formulation 2B[b]	% (w/v)	Formulation 2C[c]	% (w/v)
Paclitaxel	1.2	Paclitaxel	7.5	Paclitaxel	7.5
TPGS[d]	40	TPGS[d]	46.8	TPGS[d]	46.8
Propylene glycol	40	Labrasol[e]	24.9	Labrafil M 1944 CS[f]	14.9
Vitamin E	0.5	Sorbitan monooleate	14.9	PEG 400	24.9
Ascorbyl palmitate	0.5	Ascorbyl palmitate	1.0	Ascorbyl palmitate	1.0
Anhydrous alcohol	17.8	Anhydrous alcohol	4.9	Anhydrous alcohol	4.9

[a] Formulation 1, oral drinking solution 15 ml

[b] Formulation 2B, liquid-filled capsule formulation 2B 0.6 ml

[c] Formulation 2C, liquid-filled capsule formulation 2C 0.6 ml

[d] TPGS, D-alpha-tocopheryl polyethylene glycol 1000 succinate

[e] Labrasol, caprylocaproyl macrogol-8 glycerides

[f] Labrafil M 1944 CS, polyoxyethylated oleic glycerides

convenient for patients than i.v. administration. However, oral treatment with paclitaxel is severely hampered because of its low bioavailability [12], which is caused by two main reasons. Firstly, paclitaxel undergoes hepatic metabolism and biliary excretion. The formation of 6α-hydroxypaclitaxel is catalysed by cytochrome P450 (CYP)2C8, while 3′p-hydroxypaclitaxel is formed via metabolism by CYP3A4, and both metabolites are further converted to 6α,3′p-dihydroxypaclitaxel [11]. Secondly, paclitaxel is a high affinity substrate for the drug efflux transporter P-glycoprotein (P-gp), which is expressed in the biliary tract and intestine [23].

The search for agents that help to restore the drug sensitivity of multidrug resistant tumour cells has led to the identification and clinical testing of potent P-gp blockers, such as cyclosporin A (CsA) [5, 20]. Previous studies carried out at our Institute revealed that co-administration of oral CsA resulted in an increased systemic exposure to oral paclitaxel [26]. As CsA is an inhibitor of both P-gp and CYP3A4, both an increased absorption and a reduced first-pass effect may be responsible for the increased systemic exposure. In a previous study it was shown that 10 mg/kg CsA was sufficient for maximal enhancement of paclitaxel bioavailability [16].

P-glycoprotein is encoded by the multidrug resistance (*MDR1*) gene. Functional genetic single nucleotide polymorphisms (SNPs) of *MDR1* may be associated with variability of paclitaxel PK in patients [3]. Hoffmeyer et al. described 15 SNPs in the human *MDR1* gene in a Caucasian population, including polymorphisms in C1236T in exon 12 and C3435T in exon 26 [9]. They observed that individuals with the homozygous TT genotype at position 3436 in exon 26 have significantly lower duodenal P-gp expression. This may influence the uptake of orally administered P-gp substrates. We determined genetic polymorphisms in exon 12, 21, and 26 of the *MDR1* gene.

In earlier studies the i.v. paclitaxel formulation containing CrEL and ethanol was ingested orally as a drink solution [13–15, 20, 21]. Although CrEL is not taken up from the gastrointestinal tract [17] it affects paclitaxel PKs by limiting the absorption of paclitaxel from the intestine after oral administration. This is probably caused by entrapment of paclitaxel in micelles, thereby reducing the availability of paclitaxel for absorption [1, 19, 22, 24, 29]. Although, many attempts have been undertaken to improve systemic exposure of paclitaxel after oral administration, thus far a favourable oral formulation has not been found.

The novel oral formulations of paclitaxel used in the current study were a drinking solution (formulation 1) and two different liquid-filled capsules (formulations 2B and 2C). All three formulations consist of different pharmaceutical ingredients and do not contain CrEL (Table 1). Furthermore, the formulations contain a lower amount of ethanol compared to the orally administered i.v. paclitaxel formulations.

The choice of the excipients used in the novel formulations was motivated by previous in vivo studies in rats in combination with CsA. In the three formulations, TPGS (D-alpha-tocopheryl polyethylene glycol 1000 succinate) has been selected for its ability to solubilize paclitaxel. TPGS is a derivative of vitamin E with amphiphilic properties and it is used as excipient in Agenerase® (amprenavir, GlaxoSmithKline, UK). TPGS has been shown to increase the bioavailability of poorly absorbed lipophilic drugs [7]. The mechanism of action of TPGS can be explained, in part, by its solubilizing effect through improved micelle formation [4]. Labrasol® (caprylocaproyl macrogol-8 glycerides), used in capsule formulation 2B, is a non-ionic amphiphilic excipient known as solubilizer and bioavailability

enhancer for poorly soluble drugs. Labrasol formulated in a liquid-filled capsule has been shown to increase the systemic exposure to UK 81252, an experimental drug with potential application as antihypertensive agent, after oral administration to dogs [6]. It was suggested that this was partly caused by a permeability enhancing effect of Labrasol. Labrafil® M 1944 CS (polyoxyethylated oleic glycerides), an excipient in capsule formulation 2C, is a biodegradable polyethylene glycol derivative used as co-surfactant in pharmaceutical systems. It is used as a vehicle in Sandimmune® Oral Solution (cyclosporine, Novartis Pharma, Switzerland).

The main purpose of this study was to investigate the PK of paclitaxel and two major metabolites of the novel formulations of paclitaxel for oral application. In addition, tolerability and safety were studied.

Patients and methods

Patient population

Patients with a histological or cytological diagnosis of advanced non-haematological cancer for whom no curative therapy existed and for whom treatment with single agent paclitaxel was considered of potential benefit were eligible for the study. Patients had to be recovered from any toxicities of prior treatment. Previous chemotherapy was allowed as long as the last treatment was at least 4 weeks prior to study entry and at least 3 weeks should have elapsed since receiving any radiotherapy.

Patients had to have acceptable haematological parameters (white blood cells $\geq 3.0 \times 10^9$/l, absolute neutrophil count $\geq 1.5 \times 10^9$/l, and platelets $\geq 100 \times 10^9$/l), hepatic function [serum bilirubin $\leq 1.5 \times$ upper limit of normal (ULN); AST and ALT $\leq 1.5 \times$ ULN or $\leq 5 \times$ ULN in case of liver metastases] and renal function (serum creatinine ≤ 2 ULN or creatinine clearance ≥ 40 ml/min as calculated by Cockcroft Gault formula), and a World Health Organization Performance Status (PS) ≤ 2. Patients were excluded if they had experienced severe toxicities on prior taxane treatment, suffered from serious intercurrent illness or active infections, bowel obstruction or motility disorders that could have influenced the resorption of drugs, and heart disease. Further exclusion criteria were concomitant use of known P-gp and CYP 3A modulating compounds and chronic use of H2-receptor antagonists or proton pump inhibitors. Female patients were excluded when breast-feeding or pregnant (confirmed by a pregnancy test before study entry). The Medical Ethics Committee of the Institute approved the study protocol and all patients gave written informed consent.

Study design

Initially nine patients were planned to be enrolled in the study and were randomly assigned to receive treatment with oral paclitaxel 180 mg as (1) drinking solution (formulation 1) or (2) capsule formulation 2B or (3) capsule formulation 2C on day 1, 8, or 15 depending on the randomization. CsA was administered orally at a dose of 10 mg/kg 30 min prior to each oral administration of paclitaxel.

Drug composition and administration

The composition of the three oral formulations of paclitaxel (IVAX Research Inc., Miami, FL, USA) is depicted in Table 1. Formulation 1, the drinking solution (180 mg paclitaxel in 15 ml), was administered orally to the patients within 2 h after dilution with tap water to 100 ml. Capsule formulation 2B and capsule formulation 2C (containing 45 mg paclitaxel in 0.6 ml each) were ingested orally as four capsules per dose with 120 ml water. CsA was administered as capsules of 50 and 100 mg each (Galena, Opava, Czech Republic).

No standard prophylactic anti-emetics were administered, but anti-emetics were allowed when the patient developed nausea and vomiting during previous treatment with paclitaxel or after prior treatment with one of the formulations in the current study. If necessary, patients were premedicated with oral granisetron (Kytril®) 1 mg approximately 1.5–2 h before the intake of paclitaxel. All patients received a light breakfast (one cracker) with each paclitaxel administration. Intake of a low-fat meal was allowed only 1 h after the intake of oral paclitaxel. If considered in their best interest, patients continued on a three-weekly schedule of i.v. paclitaxel administered at a dose of 175 mg/m^2 as 3-h infusion.

Sample collection and analysis

Blood samples for PK analysis of paclitaxel, 6α-hydroxypaclitaxel, and 3′p-hydroxypaclitaxel were collected via an indwelling catheter in 5 ml heparinized tubes after all three p.o. administrations. Samples were obtained prior to administration, and 10, 15, 30 min, and 1, 2, 3, 5, 7, 10, and 24 h after paclitaxel administration. Blood samples were centrifuged, and plasma was separated and immediately transferred into polypropylene tubes and stored at −20°C until analysis. Paclitaxel concentrations

in plasma were determined using a validated HPLC tandem mass spectrometric (MS/MS) method [25].

For determination of the CsA concentration, blood samples were collected in 5 ml EDTA tubes 1 h after paclitaxel administration (corresponding to 1.5 h after CsA administration). These values were used as a surrogate for CsA exposure. Whole blood samples were stored at 4°C until analysis using a specific fluorescence polarization immunoassay [18].

From every patient 3 ml whole blood was collected in an EDTA tube before start of the first course for determination of genetic polymorphisms of the *MDR1* gene.

Pharmacokinetics

The PK parameters of paclitaxel 6α-hydroxypaclitaxel, and 3′p-hydroxypaclitaxel were determined by non-compartmental analysis, using WinNonLin™ (version 5.0, Pharsight Corporation, Mountain View, CA, USA). The area under the plasma concentration–time curve (AUC) was determined using the linear logarithmic trapezoidal method up to the last measured concentration–time point and extrapolated to infinity ($AUC_{0-\infty}$) using the slope of the terminal part of the logarithmic concentration versus time curve (λ_z). The maximal observed drug concentration (C_{max}) and time to maximal observed drug concentration (T_{max}) were obtained directly from the experimental data. Furthermore, the terminal half-life ($t_{1/2}$) was determined.

Statistics

A univariate General Linear Model with treatment (formulations 1, 2B, and 2C) and day (1, 8, and 15) as fixed factors was applied on the logarithmic-transformed PK parameters of paclitaxel, to investigate the differences between the three study treatments using a LSD test. In addition, the effect of the moment (day 1, 8, and 15) and order of treatment were investigated. The a priori level of significance was set at 0.05. The software package Statistical Product and Service Solutions (version 12.1.1 for Windows, SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Pharmacogenetics

Genetic polymorphisms in exon 12 (C1236T), exon 21 (G2677T), and exon 26 (C3435T) of the *MDR1* gene were determined. Genomic DNA was isolated according to the method by Boom et al. [2]. Genetic polymorphisms in *MDR1* were all analysed according to slightly modified methods previously described by Hoffmeyer et al. [9] and Kim et al. [10] DNA was amplified and sequences of the PCR products were analysed on an Applied Biosystems 3100-Avant DNA sequencer. For sequence alignment Seqscape v2.1 (Applied Biosystems, Foster City, CA, USA) was used and the polymorphisms were determined using Graphical Overview of Linkage Disequilibrium software v1.1.0.0.

Table 2 Patient characteristics

No. of patients	10
Male/female	3/7
Median age, years (range)	58 (49–72)
Median PS (range)	1 (0–1)
Tumour type	
NSCL	3
Gastric	6
Bladder	1
Prior treatment	
Chemotherapy	10
Surgery	2
Radiotherapy	1

Safety

All toxicities observed were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0, 2003 (http://www.ctep.cancer.gov/forms/CTCAEv3.pdf).

Results

Patient characteristics

As one patient was not fully evaluable for PK analysis, one additional patient was included and in total ten patients were entered into the study. Patient characteristics are specified in Table 2.

Drug administration and extent of exposure

All patients, except patient 4, received all three study treatments (day 1, 8, and 15) at the single flat dose of 180 mg paclitaxel per formulation. The three formulations were administered in the following sequence: 1/2/3 to patients 3, 4, and 8, 2/3/1 to patients 2, 5, 9, and 10, and 3/1/2 to patients 1, 6, and 7. Patient 1 developed vomiting within 15 and 30 min after administration of formulation 1 on day 8. Therefore, administration of formulation 1 was repeated 7 days later with the use of pre-medication (dexamethasone 20 mg i.v. and granisetron 1 mg i.v. 30 min before CsA). Patient 4 also developed vomiting after administration of formulation 1 on day 1 and therefore administration of this

Table 3 Plasma PK parameters of paclitaxel, 6α-hydroxypaclitaxel, and 3′p-hydroxypaclitaxel after p.o. administration of paclitaxel 180 mg as formulation 1 ($n = 10$), formulation 2B ($n = 9$), and formulation 2C ($n = 9$)

Parameter	Formulation 1	Formulation 2B	Formulation 2C
Paclitaxel			
T_{max} (h)	2.0 (1.02–3.0)	1.0 (0.98–3.03)*	2.0 (0.98–5.03)
C_{max} (μg/ml)	0.42 (0.23–0.96)	0.48 (0.08–0.59)	0.39 (0.11–1.03)
$AUC_{0-\infty}$ (μg h/ml)	2.83 (1.69–5.12)	2.01 (1.57–3.04)	2.67 (1.05–3.61)
%CV of $AUC_{0-\infty}$	32	24	34
$t_{1/2}$ (h)	8.9 (6.0–16)	10.6 (7.3–20)	9.7 (7.6–11)
6α-Hydroxypaclitaxel			
T_{max} (h)	2.6 (2.0–6.9)	2.0 (2.0–5.02)	3.0 (2.0–5.03)
C_{max} (μg/ml)	0.20 (0.09–1.21)	0.24 (0.06–1.43)	0.43 (0.08–1.05)
$AUC_{0-\infty}$ (μg h/ml)	1.16 (0.31–6.89)	1.03 (0.33–9.15)	1.51 (0.54–5.48)
%CV of $AUC_{0-\infty}$	117	118	90
$t_{1/2}$ (h)	5.2 (4.7–24)	5.6 (4.0–8.4)	5.0 (4.3–7.0)
3′p-Hydroxypaclitaxel			
T_{max} (h)	3.0 (2.0–5.05)	2.0 (2.0–5.02)	3.1 (2.0–5.0)
C_{max} (μg/ml)	0.071 (0.046–0.25)	0.058 (0.015–0.13)	0.071 (0.021–0.18)
$AUC_{0-\infty}$ (μg h/ml)	0.53 (0.18–1.66)	0.40 (0.19–1.16)	0.45 (0.25–1.17)
%CV of $AUC_{0-\infty}$	66	63	56
$t_{1/2}$ (h)	6.1 (4.5–14)	5.8 (4.3–24)	6.0 (4.9–7.5)

Data are presented as median (range)

%CV % coefficient of variation

*$P < 0.05$ in comparison with formulation 2C

formulation was repeated 7 days later. Regarding patient 4, PK sampling at 24 h after administration of formulation 2B could not be performed due to the poor clinical status of the patient. Patient 4 died due to progression of disease and was therefore not able to receive treatment with formulation 2C.

PK and statistical analysis

Figure 1 depicts the plasma PK profiles of paclitaxel, 6α-hydroxypaclitaxel, and 3′p-hydroxypaclitaxel after treatment with formulation 1 ($n = 10$), formulation 2B ($n = 9$), and formulation 2C ($n = 9$). Interpatient variability in paclitaxel plasma concentrations was comparable between the formulations.

Figure 2 presents the $AUC_{0-\infty}$ (μg h/ml), C_{max} (μg/ml), and T_{max} (h) of paclitaxel after the three different oral formulations. The plasma PK parameters (median and range) of paclitaxel after the three study treatments are given in Table 3.

Mean $AUC_{0-\infty}$ and SD of paclitaxel was 2.89 ± 0.25 μg h/ml (3.38 ± 0.29 μM h), 2.10 ± 0.27 μg/ml (2.46 ± 0.32 μM h), and 2.50 ± 0.27 μg/ml (2.93 ± 0.32 μM h) after formulations 1, 2B, and 2C, respectively. $AUC_{0-\infty}$ of paclitaxel was not significantly different between formulations 1 and 2B ($P = 0.10$) and was also comparable for the other formulations. In addition, mean C_{max} of paclitaxel was comparable between the three formulations and was 0.46 ± 0.06 μg/ml (0.54 ± 0.07 μM), 0.40 ± 0.07 μg/ml (0.47 ± 0.08 μM), and 0.42 ± 0.07 μg/ml (0.49 ± 0.08 μM) after formulations 1, 2B, and 2C, respectively. In addition, T_{max} of paclitaxel after formulation 2B (1.6 ± 0.29 h) was substantially lower compared to formulation 2C (2.7 ± 0.3 h, $P = 0.01$). The effect of day and the interaction of day and treatment were not significant.

The mean $AUC_{0-\infty}$ ratio of 6α-hydroxypaclitaxel/paclitaxel after formulations 1, 2B, and 2C was 0.61, 1.2, and 0.91, respectively, while the AUC ratio of 3′p-hydroxypaclitaxel/paclitaxel after these formulations was 0.23, 0.20, and 0.21, respectively.

The median concentration of CsA at 1.5 h after administration was 1.08 (0.17–1.99), 1.82 (0.97–2.25), and 1.32 (0.47–2.54) μg/ml after co-administration with oral paclitaxel as formulations 1, 2B, and 2C, respectively. These results suggest that exposure to CsA was comparable between the different formulations.

Pharmacogenetics

Patients 2 and 5 had a homozygous T/T allele expressed in exon 26 and these patients also had homozygous SNPs in exon 12 and 21. A total of eight patients (80%) had heterozygous C/T allele expression in exon 26.

Safety evaluation

Overall, the formulations were well tolerated. Little NCI CTCAE Grade 1–2 non-haematological toxicities were observed, consisting mainly of gastrointestinal

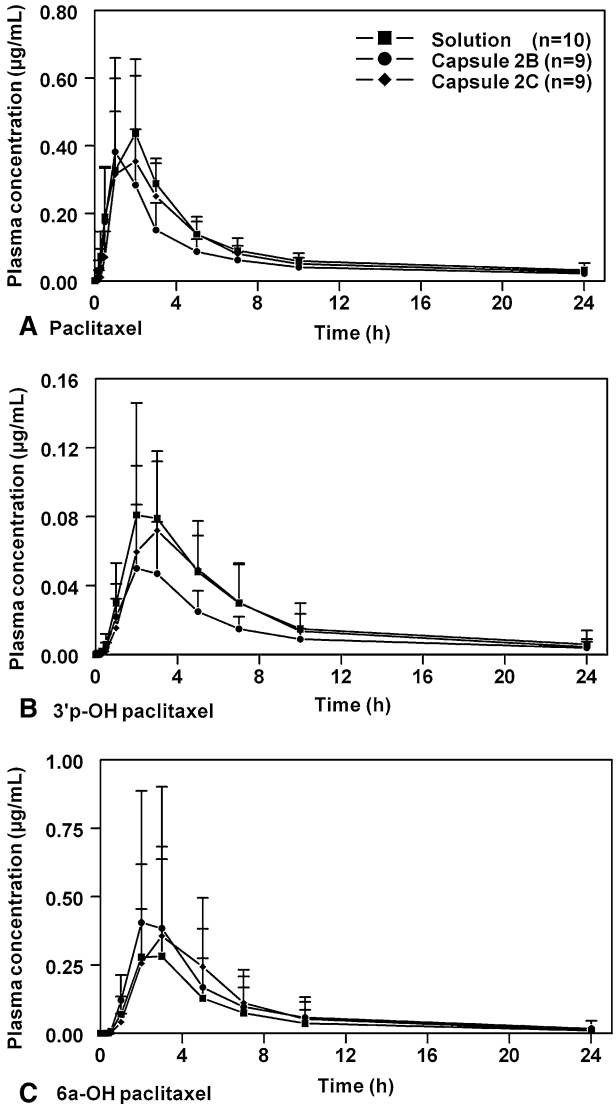

Fig. 1 Paclitaxel plasma concentration versus time curves after p.o. paclitaxel 180 mg co-administered 30 min after p.o. CsA 10 mg/kg as formulation 1 ($n = 10$), formulation 2B ($n = 9$), and formulation 2C ($n = 9$). Data are represented as mean ± SD on a semi-logarithmic scale

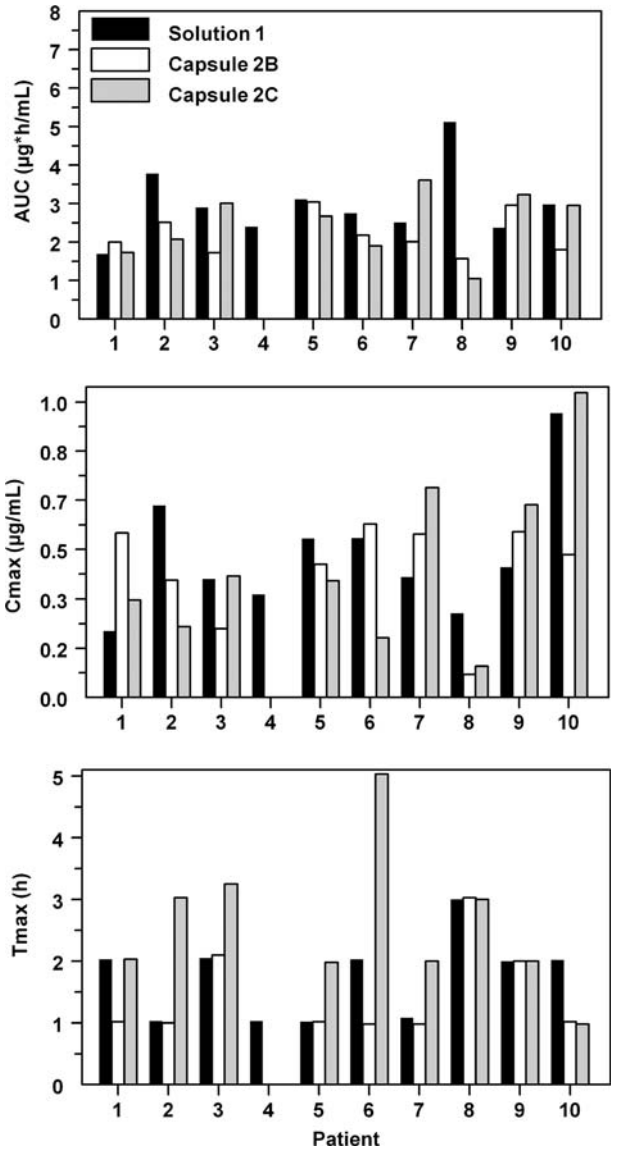

Fig. 2 Individual $AUC_{0-\infty}$, C_{max}, and T_{max} values of paclitaxel after oral treatment with formulation 1 ($n = 10$), formulation 2B ($n = 9$), and formulation 2C ($n = 9$). All three paclitaxel formulations were administered 30 min after p.o. CsA 10 mg/kg

disorders with the most common symptoms of nausea and vomiting; nausea was observed in five patients after both formulations 1 and 2B, and occurred in six patients after formulation 2C. Vomiting was observed in seven patients, six patients, and five patients after administration of formulations 1, 2B, and 2C, respectively. Five Grade 3 events were observed, consisting of nausea in patient 1 after formulation 1, and somnolence in patient 6 after all three administrations together with fatigue after formulation 2C. No life threatening adverse events (Grade 4) were reported in the study. Furthermore, no clinical relevant haematological toxicities occurred after the three treatments. In addition, no abnormal blood chemistry values were reported.

Discussion

We studied the PK of paclitaxel and two major metabolites of three novel formulations (one drinking solution and two capsules) for oral administration of paclitaxel 180 mg in combination with CsA 10 mg/kg. In addition, tolerability and safety were studied.

The release profile of paclitaxel from the formulations used in this study as well as the safety was

previously tested in preclinical studies. It was observed from in vitro studies that propylene glycol solubilized the paclitaxel and Labrasol and Labrafil M 1944 CS helped keeping the paclitaxel in solution after dilution in simulated gastric fluid. Furthermore, in vivo studies in rats demonstrated that oral administration of formulations 2B and 2C resulted in a prolonged release profile of paclitaxel without causing an initially high C_{max} of paclitaxel (data on file). This was considered to be advantageous as this could result in plasma concentrations at a pharmacologically relevant level for more prolonged periods of time.

In the present clinical study the systemic exposure of paclitaxel was comparable following oral administration of formulations 1, 2B, and 2C (all administered 30 min after CsA). Furthermore, the systemic exposure of paclitaxel after these oral formulations was comparable with recently tested novel oral paclitaxel formulations [30, 31] and with paclitaxel PK after i.v. administration of docosahexaenoic acid-paclitaxel [33]. The $AUC_{0-\infty}$ ratio of 6α-hydroxypaclitaxel/3′p-hydroxypaxlitaxel after formulations 1, 2B, and 2C was approximately 3, 6, and 4, respectively, which is comparable with previous findings [21]. The differences in paclitaxel PK between the oral formulations were low. It would be interesting, however, to investigate capsule formulation 2C in future studies because of the generally better tolerability and safety profile of a capsule formulation above an oral drink solution (formulation 1), and because of the slightly higher AUC of paclitaxel compared to formulation 2B.

It is known that CrEL, which is present in the i.v. paclitaxel formulations, is responsible for the non-linear PKs of i.v. paclitaxel [22, 27]. This can be explained by entrapment of paclitaxel in micelles in the central compartment by CrEL, leading to a more than proportional increase in plasma paclitaxel concentrations with increasing doses. We previously described that CrEL could limit the absorption rate of paclitaxel due to encapsulation in CrEL micelles. As the concentration of CrEL in the gastrointestinal tract decreases with time due to distribution, breakdown and elimination of CrEL, more unbound paclitaxel becomes available for absorption in the systemic circulation with time and consequently the absorption rate increases [8]. The shorter T_{max} of formulation 2B could be caused by a more rapid dilution of micelles in the gastrointestinal tract due to a higher contact surface area and/or lower critical micellar concentration of the excipients.

All three formulations have the advantage that they contain a substantially lower amount of ethanol compared to orally administered i.v. paclitaxel (Taxol®) at a similar paclitaxel dose of 180 mg; the amount of administered ethanol was approximately 2.7 g (formulation 1) and 0.1 g (for both formulations 2B and 2C), while this would be 11.9 g after the orally applied i.v. paclitaxel (Taxol) formulation.

Furthermore, C_{max} values of CsA were comparable to a previous study, which demonstrated that 10 mg/kg CsA is sufficient for maximal enhancement of paclitaxel bioavailability [16].

All three formulations were well tolerated and the main toxicities of the three different formulations were mild to moderate gastrointestinal disorders (nausea and vomiting). However, the limited number of patients prohibited detailed safety analysis of the three study treatments.

The fact that patients 2 and 5, having a homozygous T/T allele expressed in exon 26 and homozygous SNPs in exon 12 and 21, did not have different PK of paclitaxel compared to the other patients also supports the notion that CsA in the doses administered leads to maximal inhibition of P-gp. However, to assess the influence of different SNPs in *MDR1* on the PK of paclitaxel, larger studies with paclitaxel administered as a single drug are warranted.

In summary, we demonstrated that three new paclitaxel formulations were well tolerated after oral administration at the given dose of 180 mg when co-administered with CsA, without induction of relevant gastrointestinal or haematological toxicity. The formulations demonstrated comparable PK of paclitaxel and metabolites. We suggest new studies especially with capsule formulation 2C to explore once daily administration of paclitaxel at higher dose levels and multiple daily dosing in order to increase the systemic exposure and to prolong exposure at therapeutic levels.

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