

A novel self-microemulsifying formulation of paclitaxel for oral administration to patients with advanced cancer

SA Veltkamp^{*1,2}, B Thijssen³, JS Garrigue⁴, G Lambert⁴, F Lallemand⁴, F Binlich⁴, ADR Huitema³, B Nuijen³, A Nol², JH Beijnen^{2,3,5} and JHM Schellens^{1,2,5}

¹Division of Experimental Therapy, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, 1066 CX Amsterdam, The Netherlands;

²Department of Medical Oncology, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, 1066 CX Amsterdam, The Netherlands;

³Department of Pharmacy and Pharmacology, The Netherlands Cancer Institute/Slotervaart Hospital, 1066 EC Amsterdam, The Netherlands; ⁴Novagali Pharma SA, 91058 Evry cedex, France; ⁵Division of Biomedical Analysis, Faculty of Pharmaceutical Sciences, University of Utrecht, 3584 CG Utrecht, The Netherlands

To explore the pharmacokinetics, safety and tolerability of paclitaxel after oral administration of SMEOF#3, a novel Self-Microemulsifying Oily Formulation, in combination with cyclosporin A (CsA) in patients with advanced cancer. Seven patients were enrolled and randomly assigned to receive oral paclitaxel (SMEOF#3) 160 mg + CsA 700 mg on day 1, followed by oral paclitaxel (Taxol[®]) 160 mg + CsA 700 mg on day 8 (group I) or vice versa (group II). Patients received paclitaxel (Taxol[®]) 160 mg as 3-h infusion on day 15. The median (range) area under the plasma concentration–time curve of paclitaxel was 2.06 (1.15–3.47) $\mu\text{g h ml}^{-1}$ and 1.97 (0.58–3.22) $\mu\text{g h ml}^{-1}$ after oral administration of SMEOF#3 and Taxol[®], respectively, and 4.69 (3.90–6.09) $\mu\text{g h ml}^{-1}$ after intravenous Taxol[®]. Oral SMEOF#3 resulted in a lower median T_{max} of 2.0 (0.5–2.0) h than orally applied Taxol[®] ($T_{\text{max}} = 4.0$ (0.8–6.1) h, $P = 0.02$). The median apparent bioavailability of paclitaxel was 40 (19–83)% and 55 (9–70)% for the oral SMEOF#3 and oral Taxol[®] formulation, respectively. Oral paclitaxel administered as SMEOF#3 or Taxol[®] was safe and well tolerated by the patients. Remarkably, the SMEOF#3 formulation resulted in a significantly lower T_{max} than orally applied Taxol[®], probably due to the excipients in the SMEOF#3 formulation resulting in a higher absorption rate of paclitaxel.

British Journal of Cancer (2006) 95, 729–734. doi:10.1038/sj.bjc.6603312 www.bjcancer.com

Published online 22 August 2006

© 2006 Cancer Research UK

Keywords: paclitaxel; cremophor-free; formulation; pharmacokinetics; safety

Currently, paclitaxel is only marketed as an intravenous (i.v.) formulation. Paclitaxel is poorly soluble in most pharmaceutical solvents, therefore, in the marketed i.v. formulation it is formulated in a 1:1 combination of the solubilising agent polyoxyethylated castor oil (Cremophor[®] EL (CrEL)) and dehydrated ethanol. CrEL has been reported to be responsible for severe hypersensitivity reactions (Webster *et al*, 1997) and the nonlinear pharmacokinetic behaviour of i.v. administered paclitaxel (Sparreboom *et al*, 1996; van Tellingen *et al*, 1999; van Zuynen *et al*, 2001a).

Oral administration of paclitaxel might be attractive because it is more convenient for patients than i.v. administration. Furthermore, oral paclitaxel administration may enable the development of treatment regimens resulting in plasma concentrations above a pharmacologically relevant level for more prolonged periods of time. However, oral treatment with paclitaxel is severely hampered because of its low bioavailability, which is caused by two main reasons. Firstly, paclitaxel is a high-affinity substrate for the efflux multidrug transporter P-glycoprotein (P-gp), which is highly expressed in the gastrointestinal tract (Sparreboom *et al*, 1997).

Secondly, paclitaxel undergoes first-pass metabolism by the gut and liver cytochrome P450 (CYP) enzymes (CYP 2C8 and CYP 3A4).

Previous studies carried out at our Institute investigated the pharmacokinetics of the i.v. paclitaxel formulation after oral administration as a drinking solution diluted with water (Meerum Terwogt *et al*, 1999; Malingré *et al*, 2000a,b; Malingré *et al*, 2001a–e) and revealed that coadministration of oral CsA resulted in an increased systemic exposure to oral paclitaxel (van Asperen *et al*, 1998; Meerum Terwogt *et al*, 1999). 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. We have shown previously that systemic exposure to paclitaxel did not increase with CsA doses higher than 10 mg kg⁻¹ (Malingré *et al*, 2001a–e).

Although CrEL was reported to exhibit no oral absorption (Malingré *et al*, 2001a–e) it affects paclitaxel pharmacokinetics by limiting the absorption of paclitaxel from the intestine after oral administration, probably by entrapment of paclitaxel in micelles, thereby reducing the availability of paclitaxel for uptake (Sparreboom *et al*, 1996; Sparreboom *et al*, 1999; Malingré *et al*, 2001a–e; van Zuynen *et al*, 2001b; Bardelmeijer *et al*, 2002). Thus far, a favourable oral formulation with paclitaxel has not been found yet.

Self-Microemulsifying Oily Formulation (SMEOF)#3 is a novel oral SMEOF of paclitaxel. The formulation consists of an isotropic mixture of oils and surfactants, which solubilise paclitaxel and spontaneously forms a microemulsion upon contact with water.

*Correspondence: Dr SA Veltkamp, Division of Experimental Therapy, Department of Medical Oncology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands; E-mail: s.veltkamp@nki.nl

Received 26 April 2006; revised 19 July 2006; accepted 21 July 2006; published online 22 August 2006

Previous *in vivo* studies in *wild-type* mice and *mdr1a/b* ($-/-$) knockout mice, which lack functional P-gp activity, showed that SMEOF#3 was a suitable delivery vehicle for oral administration of paclitaxel in combination with oral CsA (data on file). The choice of the excipients was motivated by a previous study exploring particle size, physical and chemical stability as well as cytotoxic activity *in vitro* of different formulations of paclitaxel (Gursoy *et al*, 2003). Furthermore, the physical stability was assessed of emulsions of different SMEOFs of paclitaxel after dilution in simulated gastric fluid (SGF). It was shown that after dilution of the i.v. paclitaxel (Taxol[®]) formulation in SGF, major part of the micelles was destabilised and a massive precipitation immediately occurred (data on file). This phenomenon was thought to be due to diffusion of ethanol in the SGF after which the remaining CrEL was not capable to maintain all paclitaxel in solution. SMEOF#3, however, showed a good stability for about 6 h after dilution in SGF. In SMEOF#3, tyloxapol and TPGS (d-alpha-tocopheryl polyethylene glycol 1000 succinate) have been selected for their ability to solubilise paclitaxel. Tyloxapol is a nonionic surfactant used in the product Exosurf[®] (GlaxoSmithKline, UK). Upon contact with water, tyloxapol was shown to form lyotropic liquid crystals, which are thought to contribute to the formation of microemulsions (Gershanik and Benita, 2000). Furthermore, it was shown that tyloxapol can be used as a cosolvent by increasing the solubility of paclitaxel in ethanol (Gursoy *et al*, 2003). 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 (Chang *et al*, 1996), probably by its solubilising effect through improved micelle formation (Boudreaux *et al*, 1993). As compared to the commercial paclitaxel (Taxol[®]) formulation tested orally, the main advantages of SMEOF#3 are the absence of CrEL and the significantly lower ethanol/paclitaxel ratio, which allows reducing the amount of ethanol to be administered.

The purpose of this study was to investigate the pharmacokinetics, safety and tolerability of this novel oral formulation of paclitaxel (SMEOF#3).

PATIENTS AND METHODS

Patient population

Patients with a histological or cytological diagnosis of advanced nonhaematological 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 radiotherapy.

Patients had to have acceptable haematological parameters (white blood cells (WBC) $\geq 3.0 \times 10^9 l^{-1}$, and platelets $\geq 100 \times 10^9 l^{-1}$), hepatic function (serum bilirubin $\leq 20 \mu mol l^{-1}$; AST and ALT $\leq 1.5 \times$ upper limit of normal (ULN) or $\leq 3 \times$ ULN in case of liver metastases) and renal function (serum creatinine $\leq 160 \mu mol l^{-1}$ or creatinine clearance $\geq 50 ml min^{-1}$ as calculated by Cockcroft Gault formula), and a World Health Organization (WHO) performance status (PS) ≤ 2 . Patients were excluded if they had experienced severe toxicities on prior taxane treatment, suffered from uncontrolled infectious disease, heart disease, bowel obstruction or motility disorders that could have influenced the resorption of drugs. Further exclusion criteria were concomitant use of known P-gp and CYP 3A modulating drugs 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). Patients had to be willing and able to follow the protocol requirements. The Medical

Ethics Committee of the Institute approved the study protocol and all patients gave written informed consent.

Study design

Initially six patients were planned to be enrolled in the study and were randomly assigned to two groups of treatment. Group I received a combination of oral paclitaxel (SMEOF#3) 160 mg and CsA 700 mg on day 1, followed by oral paclitaxel (Taxol[®]) 160 mg in combination with CsA 700 mg on day 8, and group II received oral paclitaxel (Taxol[®]) 160 mg in combination with CsA 700 mg on day 1, followed by oral paclitaxel (SMEOF#3) 160 mg and CsA 700 mg on day 8. CsA was administered orally at a fixed dose of 700 mg (approximately equivalent to $10 mg kg^{-1}$ CsA) 30 min prior to oral administration of paclitaxel. The patients in both groups received a single i.v. administration of paclitaxel (Taxol[®]) 160 mg as a 3-h infusion on day 15.

Drug composition and administration

The composition of SMEOF#3 (Novagali Pharma SA, Evry cedex, France) is presented in Table 1. SMEOF#3 (160 mg in 10 ml) was administered orally to the patients via a syringe within 30 min after 1:3 dilution with tap water to 40 ml resulting in a final paclitaxel concentration of $4 mg ml^{-1}$. The commercially available i.v. paclitaxel (Taxol[®]) formulation (Bristol-Myers Squibb, Syracuse, NY, USA) containing paclitaxel $6 mg ml^{-1}$, ethanol $396 mg ml^{-1}$, and CrEL $527 mg ml^{-1}$ was administered orally after dilution of 26.7 ml (160 mg) with water to 40 ml ($4 mg ml^{-1}$). The i.v. paclitaxel (Taxol[®]) formulation was administered i.v. at a fixed dose of 160 mg as 3-h infusion to all patients on day 15. CsA was administered as seven capsules of 100 mg each (Neoral[®], Novartis, Basel, Switzerland).

To prevent possible nausea and vomiting during both the treatment with oral SMEOF#3 and oral Taxol[®], patients were premedicated with oral granisetron (Kytril[®]) 1 mg approximately 2 h before the intake of paclitaxel. In addition, patients received a light standard breakfast (two crackers and a cup of tea) at least 2 h prior to each paclitaxel administration. Intake of food was not allowed until 2 h following the intake of oral paclitaxel. Patients were premedicated with dexamethasone 20 mg p.o. 8–10 h prior to, and ranitidine 50 mg i.v., clemastine 2 mg i.v. and dexamethasone 20 mg i.v., 30–60 min before i.v. paclitaxel dosing, to prevent infusion-related hypersensitivity reactions. If considered in their best interest, patients continued on a 3-weekly schedule of i.v. paclitaxel at a dose of $175 mg m^{-2}$.

Sample collection and analysis

Blood samples for pharmacokinetic analysis of paclitaxel were collected via an indwelling catheter in 5 ml heparinised tubes after both p.o. and i.v. administration. Following oral administration samples were obtained prior to administration, immediately after administration, and 15, 30, 45 min, and 1, 2, 4, 6, 8, 24, 48, and 72 h after paclitaxel administration. Following i.v. administration

Table 1 Composition of SMEOF#3

Component	% (w v ⁻¹)	Function
Paclitaxel	1.6	Active substance
Vitamin E	5	Oil
TPGS ^a	30	Surfactant, cosolvent
Tyloxapol	30	Surfactant, cosolvent
Ethanol (anhydrous)	33.38	Solvent
Citric acid (anhydrous)	0.02	pH adjuster
Total	100	

^aD alpha-tocopheryl polyethylene glycol 1000 succinate.

samples were obtained prior to administration, 60, 120, and 165 min after start of infusion, at the end of infusion, and 15, 30, 45 min, and 1, 2, 4, 6, 8, 24, 48, and 72 h after infusion. 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 high performance liquid chromatographic (HPLC) tandem mass spectrometric (MS/MS) method (Vainchtein *et al*, 2006).

For the pharmacokinetic analysis of CsA, blood samples were collected in 5 ml EDTA tubes at the same time points as for paclitaxel after the oral SMEOF#3 and oral Taxol[®] administrations. Whole blood samples were stored at 4°C until analysis using a specific fluorescence polarisation immunoassay (FPIA) (Malingré, 2001).

Urine samples were collected prior to paclitaxel administration and at the intervals: 0–24, 24–48, and 48–72 h after oral SMEOF#3 and oral Taxol[®] and after i.v. Taxol[®] administration. A volume of 19 ml of each urine sample was mixed with 1 ml of a mixture of 5% CrEL (Sigma, Prague, Czech Republic) – ethanol (Merck, Darmstadt, Germany) 1:1 v v⁻¹ to prevent paclitaxel precipitation. Subsequently, 5 ml was transferred into a 10 ml polypropylene tube and stored at -20°C until analysis. Paclitaxel concentrations in urine were determined using a validated HPLC method with ultraviolet (UV) detection (Huizing *et al*, 1995).

Pharmacokinetics

The pharmacokinetic parameters of paclitaxel and CsA were determined by noncompartmental 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 ($\text{AUC}_{0-\infty}$) using the slope of the terminal part of the logarithmic concentration vs time curve (λ_z). Furthermore, the terminal half-life ($t_{1/2}$) was determined. The maximal observed drug concentration (C_{max}) and time to maximal observed drug concentration (T_{max}) were obtained directly from the experimental data.

The apparent bioavailability (F) of paclitaxel was calculated by the ratio of the $\text{AUC}_{0-\infty}$ after oral administration and $\text{AUC}_{0-\infty}$ after i.v. administration of paclitaxel. Furthermore, the fraction of the paclitaxel dose that was excreted unchanged in urine was calculated.

Statistics

The software package Statistical Product and Service Solutions (version 12.1.1 for Windows, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The priori level of significance was $P = 0.05$. The paired *t*-test was applied on logarithmic-transformed values to make a comparison between the pharmacokinetic parameters of paclitaxel after the different study treatments.

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://ctep.cancer.gov/forms/CTCAEv3.pdf>).

RESULTS

Patient characteristics

As one patient was not fully evaluable for pharmacokinetic analysis, one additional patient was included and in total seven

patients were entered into the study. Patient characteristics are specified in Table 2. Patients 1, 4, 5, and 7 were assigned to group I and patients 2, 3, and 6 were assigned to group II. Four patients and three patients had a PS of 1 and 2, respectively. Age, height, and weight appeared to be equally distributed over the two treatment groups.

Drug administration and extent of exposure

All patients received all three treatments (day 1, 8, and 15) at the single flat dose of 160 mg per formulation. The i.v. administration of Taxol[®] during day 15 was temporally interrupted in patient 1 due to infusion leakage. Patient 4, a 54 years old female, developed rash and dyspnoea 15 min following i.v. paclitaxel administration. The paclitaxel infusion was terminated and 2 mg clemastine i.v. was given, which resolved the hypersensitivity reaction. Therefore, blood sampling for pharmacokinetics could not be performed and this patient was not fully eligible. Intravenous paclitaxel administration was restarted after one hour at a lower infusion rate, which did not cause any adverse reactions.

Pharmacokinetic and statistical analysis

Figure 1 depicts the plasma pharmacokinetic profiles of paclitaxel after treatment with p.o. paclitaxel (SMEOF#3), p.o. paclitaxel (Taxol[®]) ($n = 7$), and i.v. paclitaxel (Taxol[®]) 160 mg as 3 h infusion ($n = 6$). Interpatient variability in paclitaxel plasma concentrations was comparable between p.o. SMEOF#3 and

Table 2 Patient characteristics

No. of patients	7
Male/female	5/2
Median age, years (range)	56 (29–63)
Median PS (range)	1 (1–2)
Tumour type	
NSCL	1
Stomach	1
Neuroendocrinal	1
Thyroid	1
Oesophagus cardia	2
Parotid gland	1
Prior treatment	
Surgical therapy	5
Chemotherapy	7
Radiotherapy	4

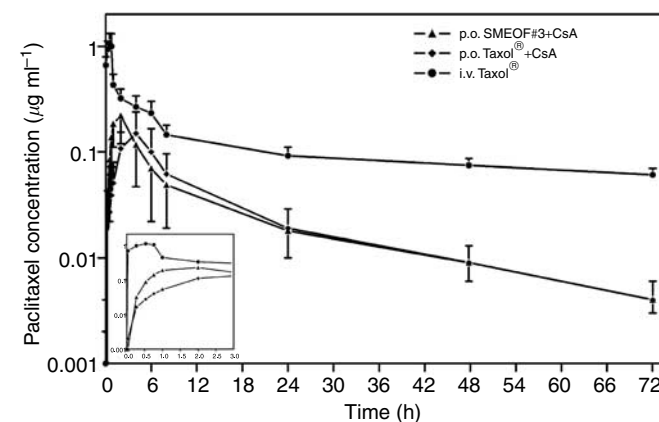


Figure 1 Paclitaxel plasma concentration vs time curves after p.o. SMEOF#3 160 mg + CsA 700 mg, p.o. Taxol[®] 160 mg + CsA 700 mg ($n = 7$), and i.v. Taxol[®] 160 mg as 3 h infusion ($n = 6$). Data are represented as mean \pm s.d. on a semi-logarithmic scale.

p.o. Taxol[®], both coadministered with CsA, but was lower after i.v. administered Taxol[®].

Figure 2 presents the $AUC_{0-\infty}$ ($\mu\text{g h ml}^{-1}$), C_{max} ($\mu\text{g ml}^{-1}$), and T_{max} (h) of paclitaxel after p.o. SMEOF#3, p.o. Taxol[®] and after i.v. Taxol[®] given as 3 h infusion. T_{max} after oral SMEOF#3 was substantially lower compared to p.o. paclitaxel (Taxol[®]) ($P=0.021$).

The plasma pharmacokinetic parameters of paclitaxel after the three study treatments are depicted in Table 3. The median (range) $AUC_{0-\infty}$ of the SMEOF#3 formulation was 2.06 (1.15–3.47) $\mu\text{g h ml}^{-1}$, which was not significantly higher than the $AUC_{0-\infty}$ of 1.97 (0.58–3.22) $\mu\text{g h ml}^{-1}$ after oral Taxol[®] ($P=0.74$). The interpatient variability in $AUC_{0-\infty}$ was relatively high after both p.o. SMEOF#3 (%CV=42) and p.o. Taxol[®] (%CV=45). Furthermore, oral SMEOF#3 resulted in a not significantly higher median C_{max} of 0.21 (0.15–0.35) $\mu\text{g ml}^{-1}$ compared to a C_{max} of 0.16 (0.10–0.29) $\mu\text{g ml}^{-1}$ after oral Taxol[®] ($P=0.15$). Remarkably, oral SMEOF#3 showed a significantly lower T_{max} of 2.0 (0.5–2.0) h than p.o. Taxol[®], which had a T_{max} of 4.0 (0.8–6.1) h ($P=0.021$). The median apparent bioavailability

was 40% (19–83%) and 55% (9–70%) for the oral SMEOF#3 and oral Taxol[®] formulation, respectively. After both i.v. and oral administration excretion of paclitaxel in the urine was low and more than 70% of the total urinary excretion occurred within 24 h.

Figure 3 depicts the mean pharmacokinetic profiles of CsA after oral administration of CsA 700 mg in combination with p.o. SMEOF#3 160 mg and p.o. Taxol[®] 160 mg ($n=7$). The pharmacokinetic parameters of CsA of all three study treatments are summarised in Table 4.

Figure 3 and Table 4 clearly show that CsA pharmacokinetics were not influenced by coadministration of either paclitaxel formulations.

Safety evaluation

Nonhaematological toxicities were CTCAE grade 1–2, except for two grade 3 events: one hypersensitivity reaction in patient 4 after i.v. paclitaxel administration, and muscular weakness in patient 1,

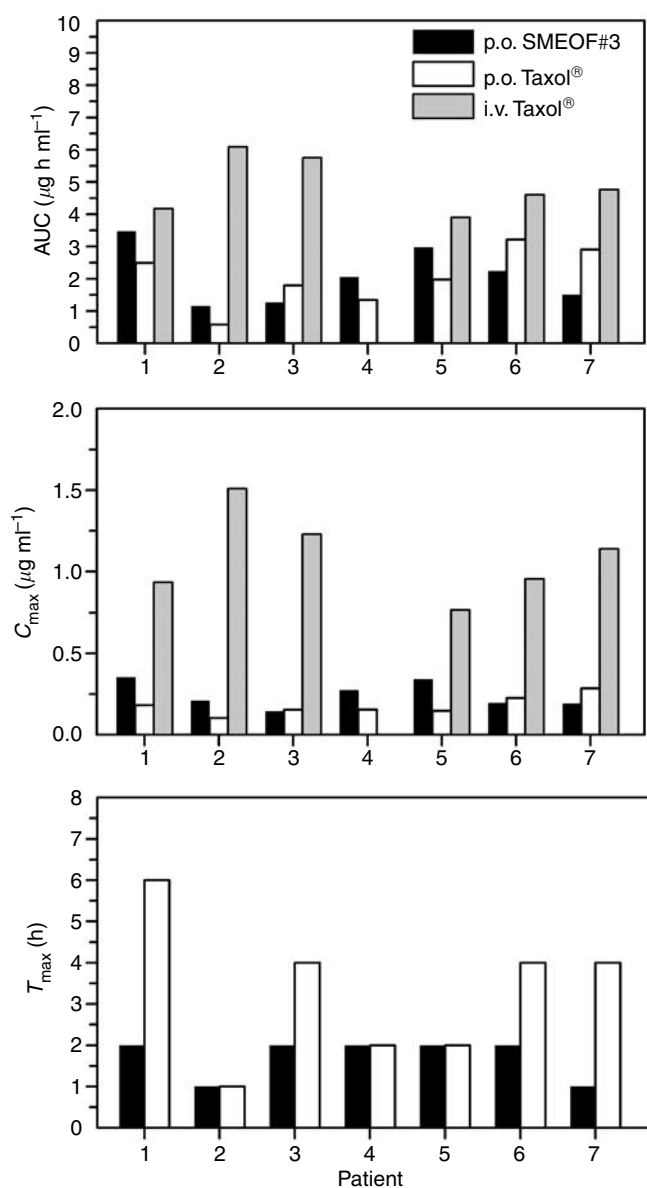


Figure 2 Individual $AUC_{0-\infty}$, C_{max} , and T_{max} values of paclitaxel after treatment with p.o. SMEOF#3 and p.o. Taxol[®] ($n=7$), both coadministered with CsA, and after treatment with i.v. Taxol[®] ($n=6$).

Table 3 Plasma pharmacokinetic parameters of paclitaxel after p.o. SMEOF#3 160 mg, p.o. Taxol[®] 160 mg ($n=7$), and i.v. Taxol[®] 160 mg as 3 h infusion ($n=6$)

Parameter	SMEOF#3 p.o.	Taxol [®] p.o.	Taxol [®] i.v.
T_{max} (h)	2.0 (0.5–2.0)	4.0 (0.8–6.1)	NA
C_{max} ($\mu\text{g ml}^{-1}$)	0.21 (0.15–0.35)	0.16 (0.10–0.29)	1.05 (0.77–0.15)
$AUC_{0-\infty}$ ($\mu\text{g h ml}^{-1}$)	2.06 (1.15–3.47)	1.97 (0.58–3.22)	4.69 (3.90–6.09)
%CV of AUC	42	45	18
$t_{1/2}$ (h)	23 (20–28)	22 (17–33)	23 (16–32)
F(%)	40 (19–83)	55 (9–70)	
%CV of F	59	48	
U_{excr} (% of dose) ^a	1.3 (0.5–2.1)	1.7 (0.6–3.6)	5.0 (3.4–8.3)

Data are presented as median (range). NA, not applicable. ^a U_{excr} , urinary paclitaxel excretion. %CV % coefficient of variation.

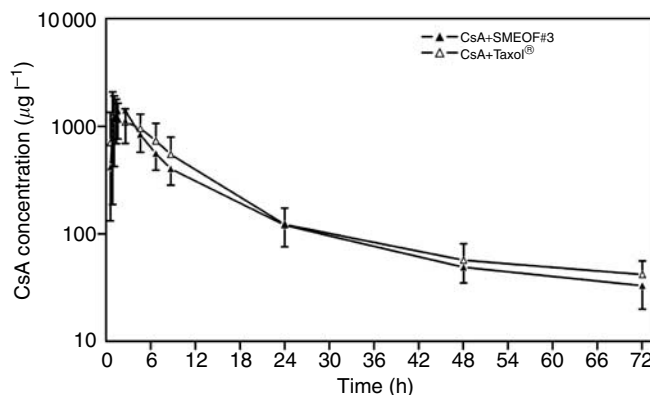


Figure 3 CsA blood concentration vs time curves after administration of CsA 700 mg in combination with oral SMEOF#3 and oral Taxol[®] ($n=7$). Data are represented as mean \pm s.d. on a semi-logarithmic scale.

Table 4 Plasma pharmacokinetic parameters of CsA after administration of CsA 700 mg in combination with p.o. SMEOF#3 160 mg and p.o. Taxol[®] 160 mg ($n=7$)

Parameter	SMEOF#3	Taxol [®]
T_{max} (h)	2.6 (0.8–2.8)	1.5 (0.8–6.7)
C_{max} ($\mu\text{g ml}^{-1}$)	1.48 (0.86–2.89)	1.51 (0.80–2.71)
$AUC_{0-\infty}$ ($\mu\text{g h ml}^{-1}$)	13.3 (10–23.8)	15.8 (8.95–25.1)
%CV of AUC	32	34
$t_{1/2}$ (h)	17 (12–28)	20 (8–34)

Data are presented as median (range).

that was considered to be probably related to SMEOF#3. No life threatening adverse events (grade 4) and deaths (grade 5) were reported in the study. Overall, the most frequently reported drug-related adverse events were gastrointestinal disorders with the most common symptoms of nausea occurring in three patients after oral administration of paclitaxel. Furthermore, abdominal pain, diarrhoea, and stomatitis were reported in two patients. No clinical relevant haematological toxicities occurred after the three treatments. Furthermore, no abnormal blood chemistry values were reported.

DISCUSSION

In the present clinical study, we tested the pharmacokinetics, safety and tolerability of SMEOF#3, a new micro-emulsifying formulation for oral administration of paclitaxel in combination with CsA.

The apparent bioavailability of paclitaxel after oral administration of SMEOF#3 coadministered with CsA was estimated at 40% (19–83%) and was comparable to the apparent bioavailability of orally administered Taxol[®]. These data were in line with studies that showed that the apparent bioavailability of orally administered Taxol[®] in combination with CsA was approximately 47% (Huizing *et al*, 1997; Meerum Terwogt *et al*, 1999).

The term bioavailability, however, should be interpreted with caution due to the nonlinear pharmacokinetics of i.v. paclitaxel caused by the presence of CrEL (van Tellinggen *et al*, 1999). Entrapment of paclitaxel in CrEL micelles in the central compartment causes a more than proportional increase in plasma paclitaxel concentrations with increasing doses. Studies in mice showed that these higher total drug levels in plasma did not result in higher drug levels in tissues (Sparreboom *et al*, 1996). Previous studies showed that CrEL is not absorbed after oral administration. This pseudo-nonlinearity of i.v. paclitaxel has two important implications for the pharmacology of oral paclitaxel. Firstly, the oral bioavailability of paclitaxel, calculated by comparing the AUC values after oral and i.v. administration, will be underestimated as the affinity of paclitaxel for the plasma compartment is increased after i.v. administration due to the presence of CrEL in the central circulation. Secondly, the pseudo-nonlinearity of i.v. paclitaxel implies that after oral administration, when CrEL is not present, plasma levels of paclitaxel represent a higher fraction of free drug, which will result in enhancement of the availability of paclitaxel for the (tumour) tissues (van Tellinggen *et al*, 1999). Consequently, threshold values for the paclitaxel concentration established for i.v. paclitaxel (Gianni *et al*, 1995; Huizing *et al*, 1997) cannot be used for oral administration of paclitaxel.

The pharmacokinetic parameters of CsA after coadministration with oral SMEOF#3 and orally administered Taxol[®] were

comparable. Furthermore, pharmacokinetic parameters of CsA were in line with those obtained before (Malingré *et al*, 2001a–e). It has been demonstrated that 10 mg kg⁻¹ CsA was sufficient for maximal enhancement of paclitaxel bioavailability (Malingré *et al*, 2001a–e). In combination, these facts suggest that a dose of 700 mg CsA as used in this study was sufficient.

Remarkably, the T_{max} of paclitaxel after oral administration of the SMEOF#3 formulation was lower compared to oral Taxol[®]. It was previously described by us that CrEL limits 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 (de Jonge *et al*, 2005). The lower T_{max} after oral SMEOF#3 is probably due to the ability of the SMEOF#3 formulation to remain stable in the gastrointestinal tract avoiding precipitation of paclitaxel leading to a major fraction of paclitaxel in solution, which is available for absorption. However, in the case of oral paclitaxel administered as Taxol[®], probably a significant amount of paclitaxel precipitates due to quick diffusion and resorption of ethanol and the precipitated fraction of paclitaxel is slowly re-dissolved in the gastrointestinal fluids before being absorbed. Furthermore, a lower amount of ethanol was administered after SMEOF#3 160 mg compared to the orally applied i.v. paclitaxel (Taxol[®]) formulation 160 mg; the amount of administered ethanol was approximately 3.3 g and 10.6 g after SMEOF#3 and the orally applied i.v. paclitaxel (Taxol[®]) formulation, respectively.

An extensive pharmacokinetic analysis demonstrated an increase in the systemic exposure to paclitaxel and a prolonged time of a paclitaxel concentration above a pharmacological relevant level with increasing doses of SMEOF#3 (data not shown).

In summary, we demonstrated that the novel SMEOF#3 formulation was well tolerated after oral administration at the given dose of 160 mg when coadministered with CsA, without induction of relevant gastrointestinal or haematological toxicity. Regarding the nearly uneventful oral administration of the 160 mg dose together with the relatively low AUC_{0–∞} after CsA coadministration, we suggest that new studies should be initiated with this novel SMEOF#3 formulation to explore once daily administration of paclitaxel at higher dose levels in order to increase systemic exposure and to prolong exposure at therapeutic levels.

ACKNOWLEDGEMENTS

We thank Ms Ciska Koopman for her analytical support.

REFERENCES

- Bardelmeijer HA, Ouwehand M, Malingré MM, Schellens JHM, Beijnen JH, van Tellinggen O (2002) Entrapment by Cremophor EL decreases the absorption of paclitaxel from the gut. *Cancer Chemother Pharmacol* **49**: 119–125
- Boudreaux JP, Hayes DH, Mizrahi S, Maggiore P, Blazek J, Dick D (1993) Use of water-soluble liquid vitamin E to enhance cyclosporine absorption in children after liver transplant. *Transplant Proc* **25**: 1875
- Chang T, Benet LZ, Hebert MF (1996) The effect of water-soluble vitamin E on cyclosporine pharmacokinetics in healthy volunteers. *Clin Pharmacol Ther* **59**: 297–303
- de Jonge ME, Huitema ADR, Schellens JHM, Rodenhuis S, Beijnen JH (2005) Population pharmacokinetics of orally administered paclitaxel formulated in Cremophor EL. *Br J Clin Pharmacol* **59**: 325–334
- Gershnik T, Benita S (2000) Self-dispersing lipid formulations for improving oral absorption of lipophilic drugs. *Eur J Pharm Biopharm* **50**: 179–188
- Gianni L, Kearns CM, Giani A, Capri G, Vigano L, Lacatelli A, Bonadonna G, Egorin MJ (1995) Nonlinear pharmacokinetics and metabolism of paclitaxel and its pharmacokinetic/pharmacodynamic relationships in humans. *J Clin Oncol* **13**: 180–190
- Gursoy N, Garrigue JS, Razafindratsita A, Lambert G, Benita S (2003) Excipient effects on *in vitro* cytotoxicity of a novel paclitaxel self-emulsifying drug delivery system. *J Pharm Sci* **92**: 2411–2418
- Huizing MT, Giaccone G, van Warmerdam LJ, Rosing H, Bakker PJ, Vermorken JB, Postmus PE, van Zandwijk N, Koolen MG, ten Bokkel Huinink WW, van der Vijgh WJ, Bierhorst FJ, Lai A, Dalesio O, Pinedo HM, Veenhof CH, Beijnen JH (1997) Pharmacokinetics of paclitaxel and carboplatin in a dose-escalating and dose-sequencing study in patients with non-small-cell lung cancer. The European Cancer Centre. *J Clin Oncol* **15**: 317–329
- Huizing MT, Rosing H, Koopman F, Keung AC, Pinedo HM, Beijnen JH (1995) High-performance liquid chromatographic procedures for the

- quantitative determination of paclitaxel (Taxol) in human urine. *J Chromatogr B Biomed Appl* **664**: 373–382
- Malingré MM (2001) Performance of the analytical assays of paclitaxel, docetaxel and cyclosporin in a routine hospital laboratory setting. *J Liq Chrom Rel Technol* **24**: 2697–2717
- Malingré MM, Beijnen JH, Rosing H, Koopman FJ, van Tellingen O, Duchin K, ten Bokkel Huinink WW, Swart M, Lieverst J, Schellens JHM (2001a) A phase I and pharmacokinetic study of bi-daily dosing of oral paclitaxel in combination with cyclosporin A. *Cancer Chemother Pharmacol* **47**: 347–354
- Malingré MM, Beijnen JH, Rosing H, Koopman FJ, van Tellingen O, Duchin K, ten Bokkel Huinink WW, Swart M, Lieverst J, Schellens JHM (2001b) The effect of different doses of cyclosporin A on the systemic exposure of orally administered paclitaxel. *Anticancer Drugs* **12**: 351–358
- Malingré MM, Beijnen JH, Schellens JHM (2001c) Oral delivery of taxanes. *Invest New Drugs* **19**: 155–162
- Malingré MM, Meerum Terwogt JM, Beijnen JH, Rosing H, Koopman FJ, van Tellingen O, Duchin K, ten Bokkel Huinink WW, Swart M, Lieverst J, Schellens JHM (2000b) Phase I and pharmacokinetic study of oral paclitaxel. *J Clin Oncol* **18**: 2468–2475
- Malingré MM, Schellens JHM, van Tellingen O, Ouwehand M, Bardelmeijer HA, Rosing H, Koopman FJ, Schot ME, ten Bokkel Huinink WW, Beijnen JH (2001d) The co-solvent Cremophor EL limits absorption of orally administered paclitaxel in cancer patients. *Br J Cancer* **85**: 1472–1477
- Malingré MM, Schellens JHM, van Tellingen O, Rosing H, Koopman FJ, Duchin K, ten Bokkel Huinink WW, Swart M, Beijnen JH (2000a) Metabolism and excretion of paclitaxel after oral administration in combination with cyclosporin A and after i.v. administration. *Anticancer Drugs* **11**: 813–820
- Malingré MM, ten Bokkel Huinink WW, Duchin K, Schellens JHM, Beijnen JH (2001e) Pharmacokinetics of oral cyclosporin A when co-administered to enhance the oral absorption of paclitaxel. *Anticancer Drugs* **12**: 591–593
- Meerum Terwogt JM, Malingré MM, Beijnen JH, ten Bokkel Huinink WW, Rosing H, Koopman FJ, van Tellingen O, Swart M, Schellens JHM (1999) Coadministration of oral cyclosporin A enables oral therapy with paclitaxel. *Clin Cancer Res* **5**: 3379–3384
- Sparreboom A, van Asperen J, Mayer U, Schinkel AH, Smit JW, Meijer DK, Borst P, Nooijen WJ, Beijnen JH, van Tellingen O (1997) Limited oral bioavailability and active epithelial excretion of paclitaxel (Taxol) caused by P-glycoprotein in the intestine. *Proc Natl Acad Sci USA* **94**: 2031–2035
- Sparreboom A, van Tellingen O, Nooijen WJ, Beijnen JH (1996) Nonlinear pharmacokinetics of paclitaxel in mice results from the pharmaceutical vehicle Cremophor EL. *Cancer Res* **56**: 2112–2115
- Sparreboom A, van Zuylen L, Brouwer E, Loos WJ, de Bruijn P, Gelderblom H, Pillay M, Nooter K, Stoter G, Verweij J (1999) Cremophor EL-mediated alteration of paclitaxel distribution in human blood: clinical pharmacokinetic implications. *Cancer Res* **59**: 1454–1457
- Vainchtein LD, Thijssen B, Stokvis E, Rosing H, Schellens JHM, Beijnen JH (2006) A simple and sensitive assay for the quantitative analysis of paclitaxel and metabolites in human plasma using liquid chromatography/tandem mass spectrometry. *Biomed Chromatogr* **20**: 139–148
- van Asperen J, van Tellingen O, van der Valk MA, Rozenhart M, Beijnen JH (1998) Enhanced oral absorption and decreased elimination of paclitaxel in mice cotreated with cyclosporin A. *Clin Cancer Res* **4**: 2293–2297
- van Tellingen O, Huizing MT, Panday VR, Schellens JHM, Nooijen WJ, Beijnen JH (1999) Cremophor EL causes (pseudo-) non-linear pharmacokinetics of paclitaxel in patients. *Br J Cancer* **81**: 330–335
- van Zuylen L, Karlsson MO, Verweij J, Brouwer E, de Bruijn P, Nooter K, Stoter G, Sparreboom A (2001a) Pharmacokinetic modeling of paclitaxel encapsulation in Cremophor EL micelles. *Cancer Chemother Pharmacol* **47**: 309–318
- van Zuylen L, Verweij J, Sparreboom A (2001b) Role of formulation vehicles in taxane pharmacology. *Invest New Drugs* **19**: 125–141
- Webster LK, Linsenmeyer ME, Rischin D, Urch ME, Woodcock DM, Millward MJ (1997) Plasma concentrations of polysorbate 80 measured in patients following administration of docetaxel or etoposide. *Cancer Chemother Pharmacol* **39**: 557–560