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ORIGINAL ARTICLE

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Pharmacological study of paclitaxel duration of infusion combined with GFR-based carboplatin in the treatment of ovarian cancer

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Abstract *Purpose*: To determine the effect on systemic pharmacology and clinical toxicity of dose and mode of administration of paclitaxel combined with carboplatin in the treatment of ovarian cancer. *Patients and methods*: A total of 18 patients were treated with a dose of carboplatin determined by GFR, to attain a target AUC of 6 or 7 mg/ml·min. The paclitaxel dose was 175 or 200 mg/m^2 administered over approximately 1 or 3 h. The duration of infusion was randomized, crossing over to the alternative treatment for the second course. Blood samples were analysed for carboplatin, paclitaxel and for the excipients of the paclitaxel formulation, ethanol and Cremophor. *Results*: Overall the three-weekly schedule of administration of the combination of carboplatin and paclitaxel was well tolerated. There were no clinical differences in the toxicities observed between courses where a 1-h infusion was used compared with those with a 3-h infusion. The target AUC of carboplatin was achieved (mean ± SD 114 ± 20% of target). Analysis of paclitaxel pharmacokinetics did not show a difference in the AUC or time above a pharmacological threshold for the two infusion durations. The peak concentration of paclitaxel obtained at the end of the infusion (9.1 vs 4.5 μg/ml), and the plasma ethanol concentration (40.0 vs 20.5 mg/dl) were higher following the shorter duration infusion. Peak concentrations of Cremophor were not different. *Conclusion*: The combination of paclitaxel at a dose of 175 mg/m^2 and carboplatin at a target AUC of 6–7 mg/ml·min can safely be administered every 3 weeks. Also, a 1-h infusion of paclitaxel has no acute clinical disadvantage over a 3-h infusion and these durations of administration are pharmacologically equivalent.

Keywords Paclitaxel · Carboplatin · Pharmacokinetics · Infusion duration

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Introduction

The addition of paclitaxel to the treatment of ovarian cancer has resulted in improved response rates and long-term survival for many patients [13]. While a standard dose, frequency and mode of administration of paclitaxel in combination with carboplatin have been established, further optimization of this regimen is still desirable. Increasing the dose intensity by reducing the treatment cycle to 3 weeks is likely to produce an improvement in tumour response. Also, a shorter infusion time for paclitaxel may offer an increase in convenience, especially given the additional delay required for premedication.

The impact of a shorter infusion time on the pharmacology of paclitaxel is unclear, although the higher concentrations achieved may result in a greater degree of neurotoxicity [11]. The magnitude of the increase in peak concentration above that seen with the usual 3-h infusion period would be amplified by any nonlinearity in the pharmacokinetics of paclitaxel. A three-compartment model, nonlinear in both elimination and distribution, has been used to describe the pharmacokinetics of paclitaxel [6, 17]. However, more recent investigations indicate that this apparent nonlinearity is an artifact of the sequestration of paclitaxel by the excipient Cremophor [18, 21], and alternative models have been suggested [10]. In many studies a linear model has been found to be sufficient to describe the pharmacokinetic data from any one individual [16], while data across a range of doses indicates some nonlinearity [6]. Certainly clearance is higher at low doses of this drug (150 mg/m^2 or less) [8] than at higher doses (175–250 mg/m^2) [16].

The current study was designed to investigate whether reduction in infusion time was associated with an increase in toxicity or a disadvantageous shift in the pharmacological exposure to paclitaxel. Carboplatin was administered as a 30-min infusion immediately after the end of the paclitaxel infusion, and dosed according to the Calvert formula [3], to achieve a target AUC. Pharmacokinetics of both drugs were determined following the standard 3-h infusion of paclitaxel or a 1-h infusion in a crossover design. Concentrations of the excipients (alcohol and Cremophor) and the incidence and duration of toxicity were compared in the two courses studied for each patient.

Methods

A group of 18 patients with ovarian cancer, who had been treated surgically, but not received any prior chemotherapy, were eligible for this study. In addition patients were required to have adequate renal, hepatic and haematological function, ECOG performance status of less than 2, and a life expectancy of at least 3 months. Patients were randomized to receive paclitaxel on their first course as either a 3-h infusion or a 1-h infusion, each followed by carboplatin as a 30-min infusion. For the second course, the alternate schedule of paclitaxel administration was used. Patient 11 was studied on three occasions with three different durations of paclitaxel administration. Dose combinations of paclitaxel and carboplatin included 175 or 200 mg/m^2 + AUC 6 mg/ml·min and 175 or 200 mg/m^2 + AUC 7 mg/ml·min. These regimens formed part of an investigation into different dose combinations on a three-weekly schedule and were not dependent on clinical status. Administration was repeated every 3 weeks, with courses three and after being administered using a 3-h paclitaxel infusion. A standard premedication regimen of dexamethasone (20 mg i.v.), chlorpheniramine (10 mg i.v.) and cimetidine (300 mg i.v.) was administered prior to each dose of paclitaxel. Details of the patients studied and the doses administered are given in Table 1.

Doses of paclitaxel were prepared from the stock solution of 6 mg/ml containing 50% Cremophor and 50% dehydrated alcohol USP. Doses were diluted to a minimum of 500 ml in 5% dextrose and administered via an inline cellulose acetate filter (0.22 μm). The infusion rate was controlled with a pump (IVAC 561, Alaris Medical Systems, San Diego, Calif.). Carboplatin was prepared according to the manufacturer's instructions and administered over 30 min after the infusion of paclitaxel.

Patients were retreated when haematological toxicity had ameliorated to grade 1 or less. Duration of toxicity was the time from treatment until toxicity was reversed. Treatment was to be discontinued in the presence of severe haematological or nonhaematological toxicity, or if disease progression occurred. Patients were assessed radiologically after three cycles of treatment and those with stable or responsive disease were allowed to continue up to a further three cycles.

Blood samples were taken at the following times following paclitaxel administration: pretreatment, and 30, 60, 65, 75, 90, 105, 120, 150, 180, 240, 300, 420, 540, 780, 1140 and 1500 min after the start of the 1-h infusion; and pretreatment, and 90, 180, 195, 210, 225, 240, 270, 300, 360, 420, 540, 660, 900, 1260, 1620 min after the 3-h infusion. Blood was collected in heparin tubes and centrifuged immediately to separate the plasma. An aliquot of each plasma sample was transferred to an Amicon Centrifee ultrafiltration unit and this was then centrifuged at 4°C to collect plasma ultrafiltrate for the assay of free platinum. All plasma and ultrafiltrate samples were frozen at –20°C prior to analysis.

Assays for paclitaxel and carboplatin (free platinum) were as described previously [16]. Ethanol concentrations in pretreatment and end-of-infusion samples were determined using a commercial assay kit (Sigma). Cremophor concentrations in end-of-infusion samples were determined by a colorimetric method described previously [2]. For carboplatin, pharmacokinetic parameters were determined by noncompartmental analysis using WinNonlin. The log-trapezoidal method was used to determine AUC.

For paclitaxel, a three-compartment model was fitted to the data using NONMEM, with a proportional error model and interindividual variation in all parameters except clearance from the central compartment which was allowed to vary both among individuals and for the same individual on the two occasions studied. Various covariate models were investigated including the influence of infusion duration and peak Cremophor and alcohol concentra-

Table 1 Patient and treatment details

Patient number	Carboplatin AUC (mg/ml·min)	Paclitaxel dose (mg/m^2)	GFR (ml/min)	Surface area (m^2)	Infusion time (min)	
					Course 1	Course 2
1	7	175	87	1.5	100	183
2	7	175	112	1.6	60[a]	180[a]
3	7	175	89	1.7	60[b]	1440[b]
4	7	175	125	1.6	60	160
5	6	175	112	1.8	115	180[a]
6	7	175	131	1.7	190	110
7	7	175	68	1.6	75	160
8	7	175	113	1.6	175	100
9	7	200	105	1.6	180	130
10	7	200	74	1.9	170	60
11[c]	7	200	140	1.5	125	180 (60)
12	7	200	94	1.7	65	170
14	6	175	76	1.8	67	176
15	6	175	111	1.6	63	169
16[d]	6	175	80	1.7	180	–
17	6	175	152	1.6	60	166
18	6	175	76	1.5	176	58
19	6	175	65	1.6	170	60

[a]Pharmacokinetics not studied and exact infusion time not recorded
[b]Hypersensitivity reaction to paclitaxel on first course
[c]Patient 11 had pharmacokinetics investigated on three courses with a 60-min infusion on course 3
[d]Patient 16 suffered rapid disease progression after one course

tions on clearance. Comparisons of 1-h and 3-h infusions were performed using a standard crossover analysis assuming equal variance and a two-sided *t*-test for comparison of groups.

Results

A total of 18 patients were recruited into the study of whom 13 received a full six courses of chemotherapy. One patient had rapidly progressive disease after one course, one patient died of neutropenic sepsis after three courses, two required dose reductions and one experienced a hypersensitivity reaction to paclitaxel. The latter patient continued treatment with a 24-h infusion of paclitaxel, experienced paraesthesia and treatment delays and required dose reduction to 150 mg/m^2. Clinical details of these patients in terms of toxicity, dose reductions and delays are provided in Table 2.

For the 1-h infusion course, there were initial problems in administration due to the viscosity of the intravenous solution, particularly in combination with the inline filter recommended. This was overcome by careful programming of the infusion pump. Infusion time for the "one-hour" course actually varied from 56 to 130 min, but was less than 80 min in 10 of 14 patients studied (Table 1).

Only two patients required significant dose reductions or delays. There was no significant difference in severity, incidence or duration of haematological toxicity between the 1-h and the 3-h infusions, although there was some evidence of cumulative toxicity comparing courses 1 and 2. The incidence of grade 3 or 4 toxicity was higher in course 2 and the time to recovery or retreatment was longer (Table 2) regardless of duration of administration. After course 2, toxicity was generally stable and the treatment was well tolerated. Patients 6, 9 and 15 experienced the most significant toxicity, but this was not associated with any pretreatment clinical characteristics. Levels of CA125, which were elevated in 12 patients, normalized on completion of six courses of treatment in nearly every case (data not shown). It was not the aim of this study to investigate the clinical efficacy of the treatment, but 8 of the 13 evaluable patients had no evidence of residual or recurrent disease at the time of their last assessment.

Carboplatin pharmacokinetic data were available on each of the two courses studied for 14 patients, with a single course of data for patient 5. Comparison of pharmacokinetic parameters between courses where paclitaxel was administered as a 1-h or a 3-h infusion showed no difference in half-life or clearance of carboplatin (Table 3). The AUC values achieved, expressed as a percentage of the target AUC, were $113 \pm 15\%$ when paclitaxel was administered as a 1-h infusion and $114 \pm 24\%$ when paclitaxel was administered as a 3-h infusion. There was no difference between the AUCs observed in course 1 compared to those in course 2.

Pharmacokinetics of paclitaxel was determined in 30 courses from 15 patients. Plasma concentrations for patient 11, who received paclitaxel over 125, 180 and

Table 2 CTC grade and duration of toxicity for courses 1 and 2 when paclitaxel was administered as a 1-h or a 3-h infusion. Patients are grouped according to whether the 1-h or the 3-h infusion was administered first. Duration was defined as the time in days from nadir to recovery or retreatment, whichever was sooner

Patient number	Order	Number of courses	WBC				ANC				Platelets			
			Course 1		Course 2		Course 1		Course 2		Course 1		Course 2	
			Grade	Duration	Grade	Duration	Grade	Duration	Grade	Duration	Grade	Duration	Grade	Duration
1	1–3	6	1	7	2	7	2	7	3	7	0		1	7
4	1–3	6	1	7	2	21	1	4	3	21	0		1	7
5[a]	1–3	3	3	9	3	23	3	9	4	6	1	9	1	9
7	1–3	6	0		1	14	2	7	4	7	0		0	
11	1–3	6	1	6	2	6	2	6	4	6	1	6	1	6
12[b]	1–3	3	2	7	1	7	3	7	1	7	1	7	2	7
14	1–3	6	1	7	2	7	2	7	3	7	0		1	7
15	1–3	6	3	6	3	35	4	6	4	35	0		2	12
17	1–3	6	0		1	7	0		3	7	1	7	1	7
2	3–1	6	0		1	7	0		1	7	0		0	
3	3–1	5	1	7	3	7	4	18	3	7	1	6	1	14
6[c]	3–1	6	1	7	3	27	1	7	4	27	1	7	3	19
8	3–1	6	0		0		2		1	7	1	7	1	7
9	3–1	6	2	13	2	34	4	6	4	27	1	14	2	14
10	3–1	6	0		3	27	0		2	20	0		2	4
16[d]	3–1	1	3	18			3	2			0			
18	3–1	6	0		0		0		0		0		0	
19	3–1	6	0		2	22	0		3	22	0		1	13

[a]Treatment delays and removed from study after three courses; recommenced on carboplatin only
[b]Patient 12 died following episode of neutropenic sepsis on course 3
[c]Treatment delays; carboplatin reduced to AUC 6 from course 3
[d]Patient 16 died with rapid disease progression following course 1

60 min on successive courses are shown in Fig. 1. Initial noncompartmental analysis of the data indicated a clear effect of infusion duration on clearance ($P = 0.001$), but the magnitude of this effect was small and possibly due to a systematic underestimation of AUC using the trapezoidal rule for the longer infusion. To substantiate the validity of this effect, and to establish the likely pharmacological significance, a formal compartmental analysis of the data was performed.

Paclitaxel pharmacokinetics was best described by a three-compartment linear model for each dataset. However, there was insufficient data to estimate the parameters of this model in every case and NONMEM was used to analyse the data and to provide individual estimates of the parameters. A model incorporating nonlinear elimination or distribution of paclitaxel, as has been suggested previously [6], was also tested, but no evidence of nonlinearity was observed in the 30 data sets available. The estimate of clearance (Cl) for each patient was significantly lower for the shorter infusion duration when Cl was allowed to vary between different courses for the same individual (Table 4, Fig. 2, $P = 0.032$), supporting the observation of the noncompartmental analysis. However, in the population model, variation in clearance could not be explained by a direct effect of either infusion length or peak concentrations of Cremophor (see below). Individual paclitaxel plasma concentration profiles, together with the three-compartment population model fitted to this data are shown in Fig. 3.

Since the time for which a threshold concentration is exceeded has been identified as the critical pharmacodynamic variable for paclitaxel, the parameter estimates obtained above were used to estimate times for the threshold of 0.05 μM [6] and 0.1 μM [9]. As shown in

Table 3 Pharmacokinetic parameters for carboplatin

	Paclitaxel duration			
	Course 1		Course 2	
	1 h	3 h	3 h	1 h
Cl (ml/min)	113 ± 19	113 ± 22	107 ± 22	98 ± 25
Vz (l)	18 ± 3	16 ± 3	19 ± 5	17 ± 3
Half-life (min)	114 ± 30	113 ± 22	126 ± 47	122 ± 20
AUC (mg/ml·min)	7.5 ± 0.8	7.8 ± 0.7	8.2 ± 1.8	8.0 ± 1.0
AUC % target	112 ± 12	113 ± 19	115 ± 28	115 ± 21

Table 4 Pharmacokinetic parameters for paclitaxel (including alcohol and Cremophor). Cl was allowed to vary between courses. Cl, V_1, Q_2, V2, Q_3 and V_3 were estimated for each individual patient course from the parameters of the population model and individual datasets. V_1, Q_2, V2, Q_3 and V_3 were not allowed to vary between courses. Alcohol and Cremophor concentrations were determined in end-of-infusion samples. Time greater than threshold concentrations in minutes

	Paclitaxel duration			
	Course 1		Course 2	
	1 h	3 h	3 h	1 h
Cmax (μg/ml)	8.51 ± 3.35	4.83 ± 1.67	4.10 ± 1.55	9.61 ± 4.43
AUC (μg/ml·min)	890 ± 269	880 ± 285	761 ± 259	1012 ± 301
Half life (min)	514 ± 171	468 ± 192	512 ± 181	528 ± 154
Cl (ml/min)	318 ± 50	311 ± 50	343 ± 60	298 ± 44
V1 (l)	10.5 ± 0.3	10.8 ± 0.2		
Q2 (ml/min)	161 ± 3	162 ± 2		
V2 (l)	13.1 ± 3.3	11.3 ± 2.0		
Q3 (ml/min)	79 ± 3	77 ± 3		
V3 (l)	53.1 ± 16.8	50.0 ± 11.7		
Time > 0.05 μM	1270 ± 222	1297 ± 278	1175 ± 246	1306 ± 230
Time > 0.1 μM	752 ± 160	822 ± 252	722 ± 183	821 ± 201
Alcohol (mg/dl)	42.0 ± 14.1	22.2 ± 12.9	19.1 ± 6.2	38.1 ± 13.9
Cremophor (μl/ml)	11.6 ± 3.5	14.2 ± 3.1	11.1 ± 2.6	14.2 ± 3.8

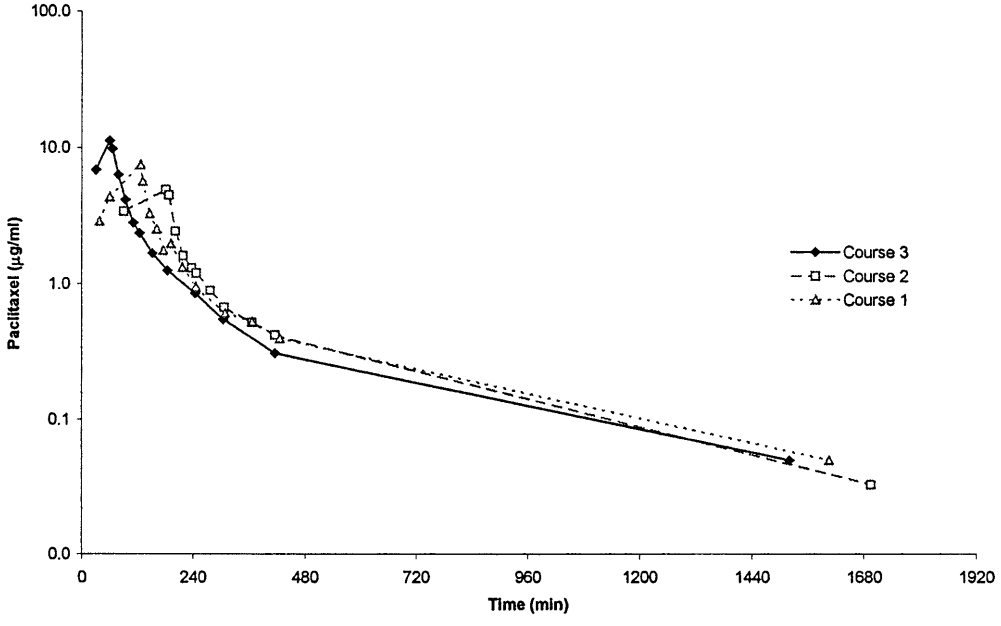


Fig. 1 Plasma concentrations of paclitaxel in patient 11 following three courses of treatment with infusion times of 125, 180 and 60 min

Table 4, there was no effect of infusion length on the time above threshold. From the previously reported relationship between time $>0.1\ \mu M$ and response duration, only four of the patients were higher than the cut-off for longer duration of response [9]. Infusion duration had no influence on this measure of the pharmacology of paclitaxel.

Shorter infusions were associated with a higher concentration of alcohol (Fig. 4a, Table 4, $P=0.0001$). The average peak concentration after the shorter infusion

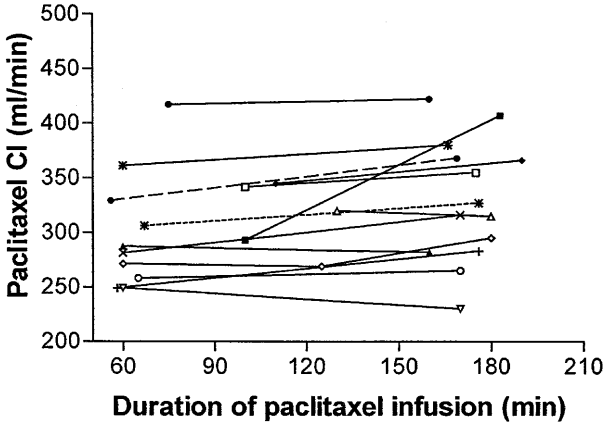


Fig. 2 The effect of infusion duration on the clearance of paclitaxel in 14 patients studied on two or more occasions. Clearance of paclitaxel estimated using NONMEM to provide a fit of a linear three-compartment population model to the data. Post-hoc estimates of individual clearances were allowed to vary between different occasions for the same individual

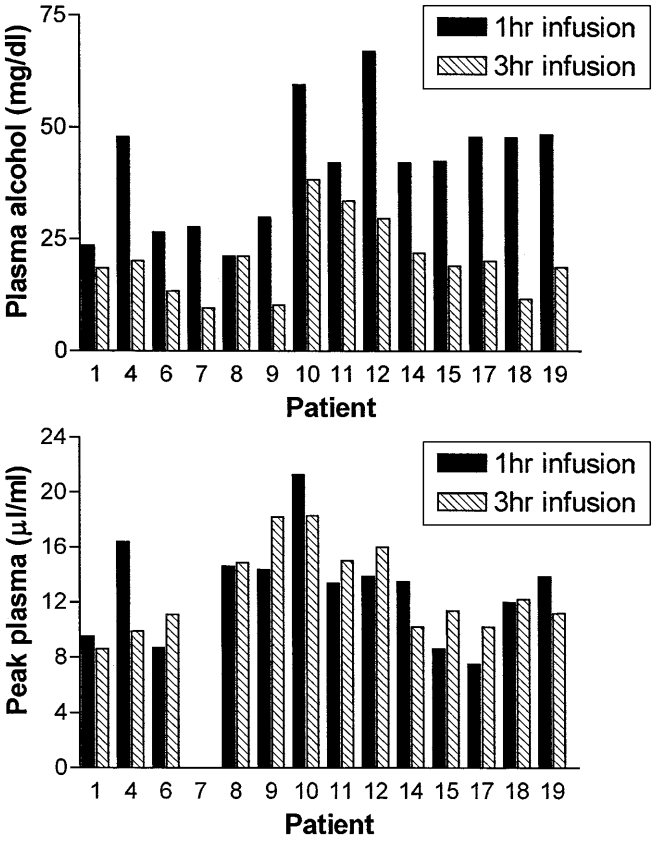
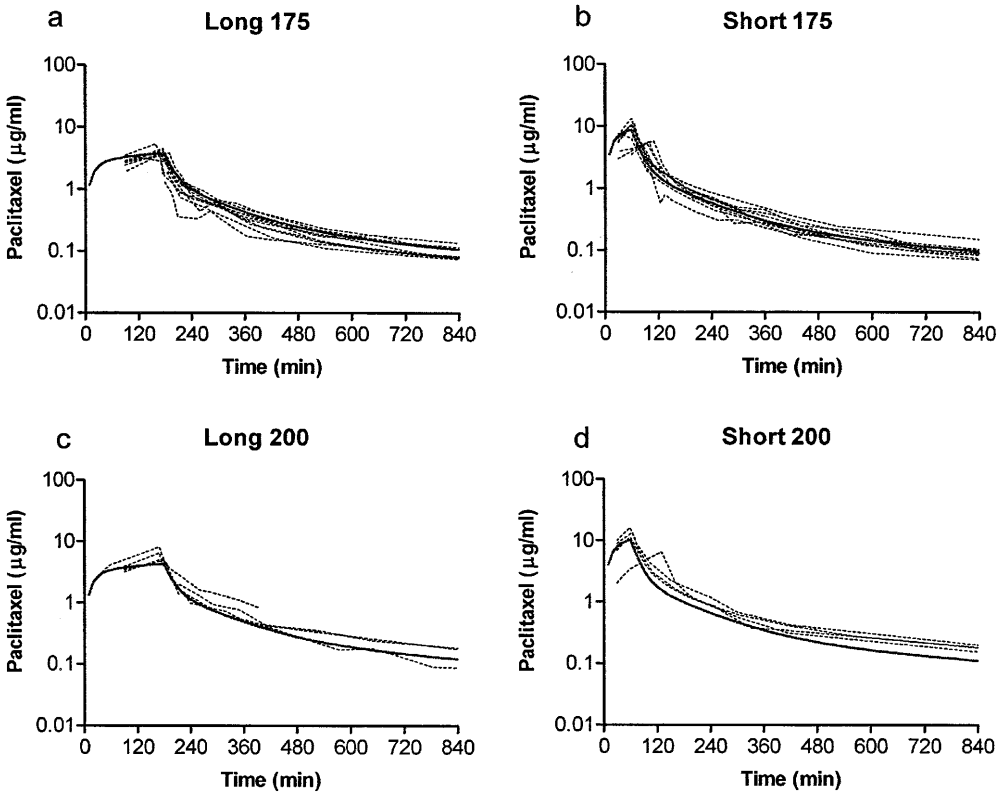


Fig. 4a, b Comparison of alcohol (*upper part*) and Cremophor (*lower part*) concentrations at the end of 1-h or 3-h infusions for patients studied on two consecutive courses. Patient 7 had insufficient sample for analysis of Cremophor

Fig. 3a–d Individual data (*faint lines*) and the predictions of the population model (*solid lines*) for paclitaxel administered as a 3-h infusion (**a, c**) or as a 1-h infusion (**b, d**) at 175 or 200 mg/m^2



was approximately half the legal limit for driving in the UK (80 mg/dl). Cremophor concentrations at the end of the infusion were not different comparing data from the short and long infusion (Fig. 4b, Table 4, $P = 0.7$). The concentrations observed are comparable to those in previous reports of Cremophor after a 1-h infusion of paclitaxel [2].

Discussion

Clinical experience with paclitaxel has established a 3-h infusion as the conventional mode of administration. Longer infusion times are associated with a greater degree of myelosuppression without any improvement in antitumour effect [4]. The administration of paclitaxel is complicated by its formulation and by the need for extensive premedication. Hypersensitivity reactions still occur, as shown by patient 3 in the current study, although these are usually overcome by increasing the duration of infusion, and further courses are often administered without difficulty. The formulation of paclitaxel in Cremophor and alcohol results in a solution that even after appropriate dilution remains rather viscous. Concerns have also been expressed regarding the clinical impact of plasma concentrations of these excipients themselves and Cremophor has been associated with complement activation [19] and hypersensitivity reactions [20]. The presence of Cremophor has been identified as a factor which influences the apparent pharmacokinetics of paclitaxel [18, 21].

All of these factors, together with concerns regarding the pharmacological and toxicity profiles resulting from shorter infusions, require careful assessment of a 1-h infusion schedule compared to a the usual 3-h infusion. To this end, a randomized crossover study of the two durations of infusion in the same patient was performed, with a comprehensive portfolio of pharmacological and toxicity evaluations.

A 1-h infusion of paclitaxel has been shown to be effective and safe in the treatment of metastatic non-small-cell lung cancer, with 200 mg/m^2 being more effective than 135 mg/m^2 [7]. Previous studies of single-agent paclitaxel administered as a 1-h infusion every 21 days have shown that neurotoxicity is dose-limiting and have found the recommended safe dose to be 225 mg/m^2 [14]. In this group of patients, AUC values were 14–35 μg/ml·h and end-of-infusion concentrations 7.5–19.2 μg/ml for doses in the range 150–250 mg/m^2 [12]. These are similar to the AUC and end-of-infusion concentrations observed in the current study (Table 4). A study of paclitaxel administered as a 1-h infusion but on a weekly schedule arrived at a MTD of 100 mg/m^2. Peak plasma concentrations of paclitaxel were 4.5 μ*M* (range 0.7–8.1 μ*M*) declining to 0.04 μ*M* (0.01–0.1 μ*M*) after 26 h [15]. Using a similar schedule, doses of 40–100 mg/m^2 per week have been administered. The AUC values reported were low (1.5–4.2 μg/ml·h), but increased linearly with dose [5]. The lower concentrations in the latter two studies reflect the more rapid elimination of paclitaxel when administered at doses below 100 mg/m^2.

In a phase I study of paclitaxel administered as a 24-h infusion, and with carboplatin given on the following day, a combination of 175 mg/m^2 and AUC 7 mg/ml·min was the recommended dose without haematological growth factors [1]. The dose combination recommended in that study is the same as that found to be most tolerable in the current patient group, using predominantly a 3-h infusion time for paclitaxel on a three-weekly treatment cycle.

A number of different models have been suggested to account for dose-dependency in the pharmacokinetics of paclitaxel. These have involved saturable elimination [17], distribution [10] or a combination of the two [6]. The influence of Cremophor has also been included in some models as this excipient may act to sequestrate the drug in plasma when present at high concentrations [18, 21]. In the population of patients studied here, no evidence of nonlinearity was observed, nor were infusion length or Cremophor concentrations found to improve the fit to the data as covariates for clearance or volume of distribution. This may be because of the narrow range of doses administered. Also, other studies that have identified nonlinear mechanisms of elimination and distribution have combined data from shorter (3 h) and longer (24 h or more) infusions. In a study of the combination of carboplatin and paclitaxel by 3-h infusion, linear pharmacokinetics for the latter drug were shown [9].

Given the increased convenience and lack of adverse pharmacological impact or toxicities, administration of a 1-h infusion of paclitaxel is preferable to the currently recommended 3-h infusion. The data presented here demonstrate that there is no disadvantage based on pharmacological investigations to using a shorter infusion duration, and the incidence of toxicity or hypersensitivity reaction was not increased. Any increased risk of neurotoxicity, which might only be seen on repeated administration, could not be assessed in the current study. The crossover design of the study allowed direct comparison of the two infusion durations in the same patient, and was most sensitive to subtle differences in the pharmacological endpoints investigated. A 1-h infusion of paclitaxel at 175 mg/m^2 could be assumed to be as effective as a 3-h infusion if used throughout a six-cycle course of treatment administered every 3 weeks in combination with carboplatin at a target AUC of 6 mg/ml·min.

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