Population pharmacokinetics of low-dose paclitaxel in patients with brain tumors

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Our aim was to assess the pharmacokinetics of a low-dose schedule of paclitaxel in combination with radiation therapy in patients with brain tumors. Eighteen patients received 20–50 mg/m^2 paclitaxel as a 1-h infusion 18–24 h before radiation with 2 Gy on 5 consecutive days. In total, 156 plasma samples from 13 patients and 38 urine samples from nine patients were collected and analyzed by a validated capillary electrophoresis method. Data analysis was done using NONMEM with a two-compartmental model and proportional error model. No signs of non-linearity in the pharmacokinetic parameters were observed in this dosing range. The median cumulative urinary excretion was 2.4% (range 0.86–7.72%) of the given dose. Plasma clearance was found to be 6.71 l/h ± 70% and central volume of distribution was 3.64 l ± 79% (population mean ± interindividual variability, respectively). At the time of the radiation, i.e. 24 h after administration with the lowest dose of 20 mg/m^2, the mean concentration of paclitaxel was 0.038 mg/l (0.045 μM) in plasma. We conclude that even with the lowest dose of 20 mg/m^2 paclitaxel, plasma concentrations at the time of radiation are achieved which are radiosensitizing *in vitro*. *Anti-Cancer Drugs* **14:417–422**

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Introduction

The treatment of gliomas and astrocytomas is insufficient, with the majority of patients dying within a few years after diagnosis [1]. Therefore, new treatment strategies are needed. Paclitaxel has shown activity against brain tumor cell lines *in vitro* and in murine xenograft models [2,3]. Furthermore, paclitaxel can cross the blood–brain barrier in brain tumor tissue, but not in intact brain tissue [4]. As the drug also displays radiosensitizing properties [5,6], treatment with low-dose paclitaxel in combination with cranial irradiation is a promising approach, as some kind of tumor selectivity can be introduced due to the limited penetration of paclitaxel into the intact brain regions. To act as a radiosensitizer, paclitaxel can be administered in a dose where no severe side-effects are expected. Zanelli *et al.* suggested a dose of 15 mg/m^2 paclitaxel daily for 5 consecutive days as a schedule sufficient to achieve radiosensitization based on *in vitro* investigations in melanoma and lung carcinoma cell lines and pharmacokinetic calculations [7]. Some response has been observed in phase I studies with paclitaxel and cranial irradiation [8,9].

The pharmacokinetics of paclitaxel have been extensively investigated in different dosing regimens [10]. Most of the later investigations focused on higher dosing regimens where paclitaxel displays non-linearity, i.e. the clearance decreases with increasing dose, resulting in a more than proportional increase in the area under the curve (AUC) and maximal concentration (C_{max}). However, this phenomenon is only apparent with higher doses and shorter infusion times [11]. There are only limited pharmacokinetic data collected with lower dosing. In an early investigation data from eight patients receiving 15–40 mg/m^2 paclitaxel with varying infusion times were presented [12]. Due to the limited assay sensitivity they could detect paclitaxel only for 2–4 h post-infusion. Thus, they possibly overestimated plasma clearance. Therefore, we collected plasma and urine samples to assess the pharmacokinetics of low-dose paclitaxel in this patient group. In particular, our aim was to calculate the plasma concentration during radiation to estimate if radiosensitizing concentrations are achieved with this low-dose schedule. A population pharmacokinetic approach was used for data analysis to reduce the number of required

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Table 1 Treatment scheme

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Paclitaxel	x	x	x	x											x	x	x	x			
Radiation			x	x	x		x									x	x	x	x	x	
Day	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	
Paclitaxel	x	x	x	x																	
Radiation			x	x	x	x	x									x	x	x	x	x	

plasma samples per patient and to get a more precise estimate of the variability.

Materials and methods

This study was approved by the local ethics committee of the University Hospital Münster. The patients gave informed consent to the blood and urine sampling.

Eighteen patients received 20–50 mg/m^2 paclitaxel as a 1-h infusion on 4 consecutive days 12–16 h before radiation with 2 Gy on 5 consecutive days. The treatment scheme is shown in Table 1. Overall, 156 plasma samples from 13 patients and 38 urine samples from nine patients were collected. Blood samples were drawn in heparinized tubes and immediately centrifuged to isolate the plasma fraction. In the protocol, plasma sampling was suggested at the end of infusion, and 0.5, 1, 2, 4, 8 and 24 h after the end of infusion. The plasma samples were stored at −20°C until analysis. Urine samples were collected in fractions up to 3, 3–8 and 8–24 h after the end of infusion. The volume of the fraction was measured and an aliquot of about 5 ml was stored at −20°C after adding 0.25 ml of Cremophor EL to stabilize the analyte because it was shown that paclitaxel is stable in frozen urine when Cremophor EL is added [13]. Plasma and urine samples were analyzed for paclitaxel using a validated capillary electrophoresis method described elsewhere [14]. The method was modified in order to reduce the required sample volume and to increase the sensitivity [15]. The limit of quantification was 0.02 mg/l (0.023 μM) with a plasma volume of 150 μl.

Available covariates were: age, height, weight, body surface area (BSA) and gender. Data analysis was done using NONMEM (version V) with the first-order conditional estimate method (FOCE) [16]. A two-compartmental model and a proportional error model were applied to the plasma data using the subroutine ADVAN 3 TRAN 4 with the parameters total plasma clearance (Cl), volume of distribution of the central compartment (V_1), intercompartmental clearance (Q) and volume of distribution of the peripheral compartment (V_2). A three-compartment model was tested using the subroutine ADVAN 11 TRAN 4. Interindividual variability was introduced into the model assuming log-normal distribution of the pharmacokinetic parameters. Inter-occasion variability (IOV), i.e. variability from one administration to the other, was introduced to the model as described by Karlsson *et al.* [17]. Model selection was done by visual inspection of plots of the data versus the population model and the individual predictions and the value of the objective function. A decrease in the objective function of more than 6.6 was considered as significant on a p level of 0.01 [18].

Table 2 Patient characteristics

	N
Patients	
total number	18
age (years)	49 (19–75)
weight (kg)	82 (60–108)
BSA (m^2)	1.97 (1.62–2.25)
gender	6F + 12M
Pharmacokinetics	
plasma samples	156 (13 patients)
urine samples	38 (9 patients)
Dosing (mg/m^2)	
20	8 patients
30	5 patients
40	4 patients
50	1 patient
Treatment cycles	
1	2 patients
2	1 patient
3	15 patients

Results

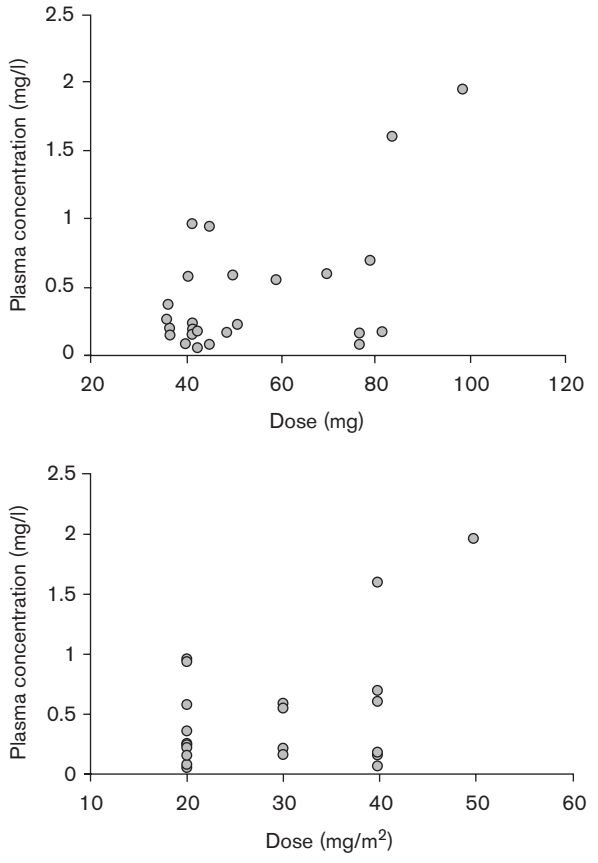
The patient's characteristics are listed in Table 2. On average, 12 plasma samples per patient were available. The number of cycles with plasma sampling was 26 with 1–7 cycles per patient. Therefore, the number of data was too small to do a non-compartmental analysis or individual curve fitting.

Initially, we investigated if there were any signs of non-linearity in the pharmacokinetic parameters. Figure 1 shows the C_{max} plotted against the absolute dose and the dose per square meter. No signs of non-linearity were apparent from this plot.

Therefore, we started the model development with a linear two-compartment model. Addition of a third compartment did not improve the fit (data not shown). Different combinations of introducing interindividual variability to the model were tested (Table 3). In

addition, covariates were included to see if they could improve the model. Some correlation was seen between BSA and the kinetic parameters. Therefore, we tested whether this parameter could improve the model. As there was no clear improvement, BSA was not included into the final model. Furthermore, IOV was tested for the ability to improve the model. As can be seen from Table 3, no clear improvement was seen.

Fig. 1



Maximal concentrations C_{max} plotted against the absolute dose and the dose per square meter.

Therefore, the best model was a two-compartment model with interindividual variability on Cl, V_1 and Q (row 2 in Table 3). Figure 2 shows the population model and the individual predictions plotted against the data. As can be seen from the plots, the data are evenly distributed around the line of identity. The data from two representative patients as well as the individual predictions of the model are shown in Fig. 3. In patients receiving the lowest dose of 20 mg/m^2, there were only five plasma samples taken from the patients at the time of radiation (Table 4). However, from the model it can be calculated that at the time of the radiation, i.e. about 24 h after administration, the mean concentration of paclitaxel is 0.038 mg/l (0.045 μM) in plasma. The clinical results of the study were published recently indicating that 50 mg/m^2 is the dose-limiting toxicity in this schedule [19,20].

To estimate the renal clearance of paclitaxel in this low-dose regimen, urine was collected at different intervals after administration. The mean urinary excretion for all patients in the first 24 h was 3.0% (range 0.86–7.72) of the given dose. Figure 4 shows the cumulative urinary excretion for all patients.

Discussion

In the literature, several different models have been suggested to describe the pharmacokinetics of paclitaxel [10]. At higher doses linear models cannot describe the distribution and elimination of paclitaxel sufficiently. This is possibly due to the vehicle Cremophor EL, which is necessary to keep paclitaxel soluble in the solutions for infusion [21]. With the low-dose schedule applied here, the kinetics can be sufficiently described using linear models. This is in agreement with earlier investigations showing that with a 1 h-infusion non-linearity is only apparent with doses higher than 150 mg/m^2 [22].

Recently, a method to distinguish between free and bound paclitaxel has been proposed [23], and successfully applied to the measurement of plasma samples after administration of paclitaxel in patients [24]. One can assume that the free fraction is thought to be the

Table 3 Development of the population pharmacokinetic model[a]

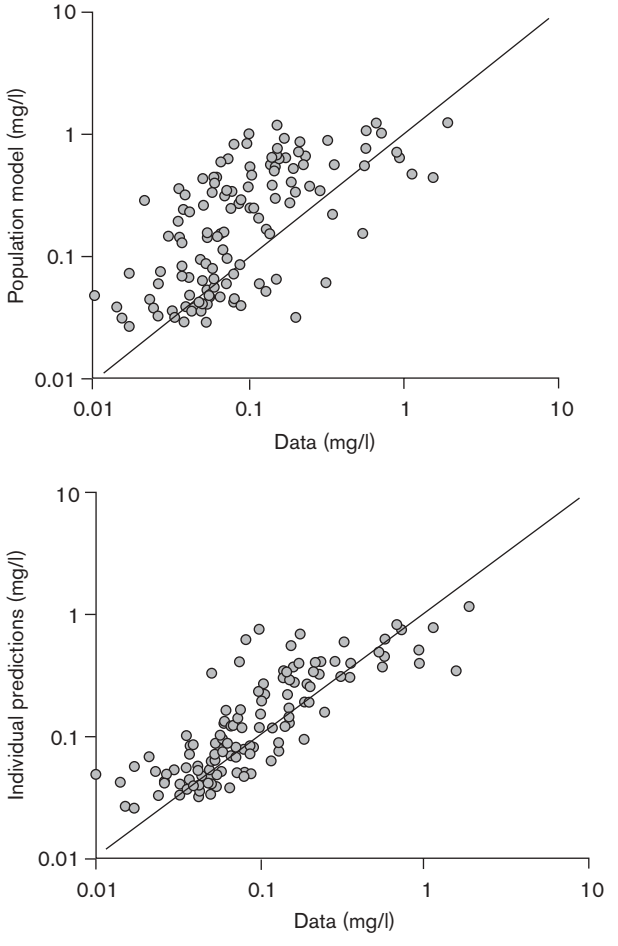
Interindividual variability	IOV	Covariate	OF	Cl (l/h)	ωCl (%)	V_1 (l)	ωV_1 (%)	V_2 (l)	ωV_2 (%)	Q (l/h)	ωQ (%)	IOV	Residual error (%)
V_1, Q, V_2			−427	7.7		45.3	44	1310	100	61.1	79		72
Cl, V_1, Q			**−434**	**6.71**	**70**	**3.64**	**79**	**881**		**44.7**	**126**		**50**
Cl, V_1			−381	25.4	65	84.1	0	414		70.6			101
Q, V_2	Cl	BSA	−419	2.51		11.4		498	90	16.9	117	125	42
Cl, Q, V_2		BSA	−414	2.83	37	19.7		754	103	27.8	75		68
Q, V_2	Cl	BSA	−435	2.54		10.6		950	88	34.1	108	123	42
V_1, Q, V_2	Q		−431	4.62		21.4		744	124	32.3	42	54	37
V_1, Q, V_2	V_1		−436	7.62		50.8	0	1660	105	65.8	85	92	74

[a]ω = interindividual variability.

pharmacologically active form. A population pharmacokinetic model was proposed describing both the bound and free fraction of paclitaxel in plasma including both linear and non-linear binding patterns of paclitaxel to different plasma components [25]. For the low concentrations present in our study, one can assume that the ratio between free and bound paclitaxel is relatively constant and that the total concentrations of paclitaxel measured here gives a useful estimate of the patient's individual exposure.

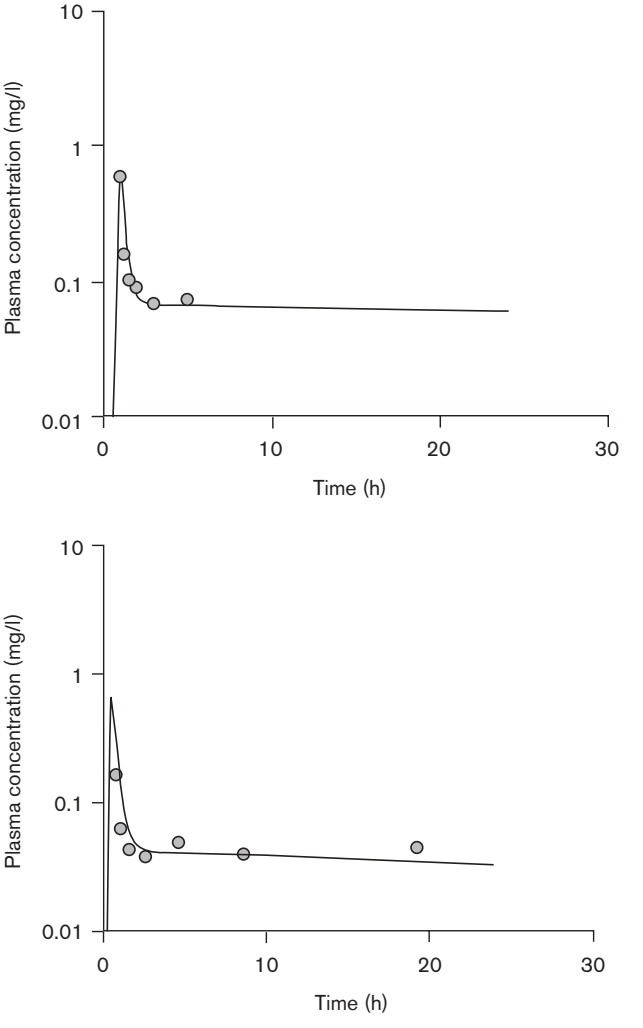
There is an ongoing discussion about the best way to adjust the dose of cytotoxic drugs in patients [26]. Dosing regimens based on BSA are often criticized in the literature [27]. In our analysis, BSA did not correlate with any of the pharmacokinetic parameters calculated. However, one has to bear in mind that the distribution of the BSA in this patient group is relatively narrow (Table 2).

Fig. 2



Goodness of fit plots for the population model and the individual predictions.

Fig. 3

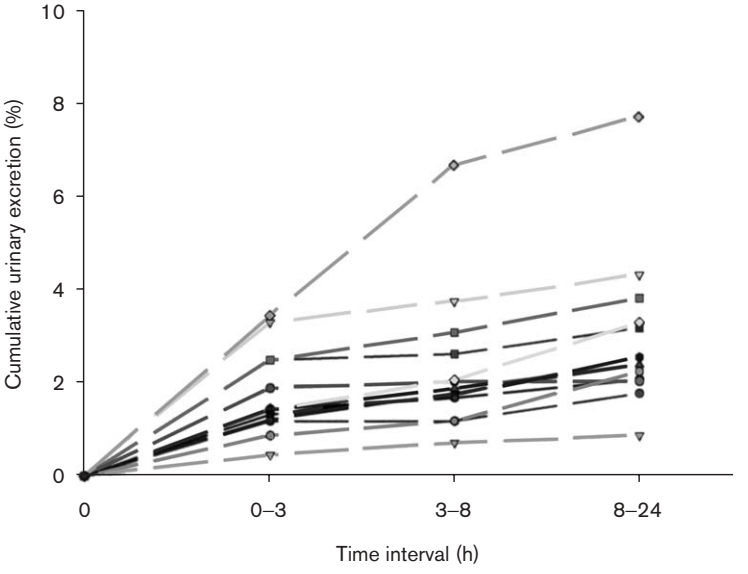


Plasma concentrations (points) and individual predictions (line) for two typical patients.

Table 4 Pharmacokinetic parameters for the patients receiving 20 mg/m^2

	Mean	CV (%)	No. of data points/samples
AUC (mg/l·h) model	7.25	43	5
C_{max} (mg/l) model	0.322	40	17
C_{max} (mg/l) data	0.328	87	17
$C_{12\,h}$ (mg/l) model	0.053	54	13
$C_{12\,h}$ (mg/l) data	0.059	40	3

Fig. 4



Cumulative urinary excretion in nine patients.

Table 5 Comparison of the results with data from the literature

	Our data	Grem *et al.* [11]	Huizing *et al.* [29]	Mross *et al.* [22]	Maier-Lenz *et al.* [30]
Dose (mg/m^2)	20–50	15–40	100	150–250	250
Cl (l/h)	6.71	53	43.1	6.85–12.8/m^2	17.0/m^2
V_1 (l)	3.64				
V_2 (l)	881	80	506	35–72/m^2 (V_{ss})	49.5/m^2 (V_{ss})
$t_{1/2\ \lambda 1}$ (h)	0.476			0.19–0.33	0.17–0.49
$t_{1/2\ \lambda z}$ (h)	108	1.5	24.9	2.79–3.22	7.8–33.5

Introduction of a parameter for variability from day to day (IOV) did not improve the model. This is mainly due to the fact that only data from one or two administrations were available for many patients. In general, this parameter enables a better estimate of the pharmacokinetic parameters. Furthermore, by comparison of the interindividual and the IOV one can decide if dose individualization is useful to reduce the variability in individual exposure [28]. In our dataset, IOV was very low, indicating that dose individualization might be possible. This finding has to be confirmed with data from patients where sampling from several repeated administrations is available.

In Table 5 we compare our data with other published pharmacokinetic data of paclitaxel in patients receiving different dosing and schedules. The only study with similar doses of paclitaxel is the investigation of Grem *et al.* reporting a high clearance of 53 (range 19-110) l/h/m^2 and a low half-life of about 1.5 h. However, the authors state that in most cases paclitaxel could only be detected up to 4 h after administration due to analytical limitations. This can result in an over-estimation of the clearance and the half-life is possibly under-estimated. Other studies were done with higher single doses in 3-weekly schedules [22,29,30]. The methodology used for the calculation of the data often differs: some studies used non-compartmental analysis [12,30], while others used individual fitting with compartmental models [22,29]. We used the population pharmacokinetic methodology in our study in order to obtain useful estimates even with a low number of plasma samples per patient. The kinetic parameters found here are similar to those of the other studies except for the terminal half-life, which is unexpectedly high in the patients reported here. However, the estimation of the terminal half-life is based only on a few number of plasma samples and should therefore be interpreted with caution.

The calculated and measured concentrations 24 h after administration indicate, assuming sufficient distribution from plasma to the tumor, that even with the lowest dose of 20 mg/m^2 the concentrations at the time of radiation are sufficient to achieve radiosensitization [7]. This is in

accordance with the clinical analysis showing that higher doses of paclitaxel were not advantageous with regard to effectiveness and outcome [20].

In the nine patients where urine samples were available, we found a median cumulative excretion of 2.4% of the given dose, indicating that renal excretion of paclitaxel plays only a minor role. Other studies found renal excretion rates between 1.4 and 8.2% [31,32]. In one study with low-dose paclitaxel, a mean of 6.6% of the total cumulative was found in the 24-h urine of two patients.

We conclude that the pharmacokinetics of low-dose paclitaxel are similar to those in standard-dose regimens. No indications for non-linear kinetics have been found. However, the long terminal half-life we found in this group of patients needs to be confirmed by more intense sampling in the terminal phase.

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