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ORIGINAL ARTICLE

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Population pharmacokinetics of ifosfamide and its 2- and 3-dechloroethylated and 4-hydroxylated metabolites in resistant small-cell lung cancer patients

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Abstract The aim of this study was to develop a population pharmacokinetic model that could describe the pharmacokinetics of ifosfamide, 2- and 3-dechloroethylifosfamide and 4-hydroxyifosfamide, and calculate their plasma exposure and urinary excretion. A group of 14 patients with small-cell lung cancer received a 1-h intravenous infusion of 2.0 or 3.0 g/m^2 ifosfamide over 1 or 2 days in combination with 175 mg/m^2 paclitaxel and carboplatin at AUC 6. The concentration-time profiles of ifosfamide were described by an ifosfamide concentration-dependent development of autoinduction of ifosfamide clearance. Metabolite compartments were linked to the ifosfamide compartment enabling description of the concentration-time profiles of 2- and 3-dechloroethylifosfamide and 4-hydroxyifosfamide. The Bayesian estimates of the pharmacokinetic parameters were used to calculate the systemic exposure to ifosfamide and its metabolites for the four ifosfamide schedules. Fractionation of the dose over 2 days resulted in increased metabolite formation, especially of 2-dechloroethylifosfamide, probably due to increased autoinduction. Renal recovery was only minor with 6.6% of the administered dose excreted unchanged and 9.8% as dechloroethylated metabolites. In conclusion, ifosfamide pharmacokinetics were described with an ifosfamide concentration-dependent development of autoinduction and allowed estimation of the population pharmacokinetics of the metabolites of ifosfamide. Fractionation of the dose resulted in increased exposure to 2-dechloroethylifosfamide, probably due to increased autoinduction.

Keywords Ifosfamide · Ifosfamide metabolites · Population pharmacokinetics · Small cell lung cancer

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Introduction

Small-cell lung cancer (SCLC) is highly sensitive to chemotherapy, but cure rates remain low with 5-year survival rates of 20–25% [11]. Responses may be followed by a rapid relapse within a few months, and this usually goes along with development of tumour resistance to chemotherapy. Since salvage treatment rarely results in long-lasting disease control, most patients die from locally progressive or metastatic disease. A paclitaxel with carboplatin regimen has been proven to show activity with a tumour response rate of 73% in resistant SCLC [9]. Brain metastases are regularly observed in SCLC patients. [22] Therefore, ifosfamide, which is also active in SCLC, was added to this regimen because its activated metabolites are able to penetrate the blood-brain barrier for 38–49% of the plasma concentrations [15].

Ifosfamide (Holoxan) is a prodrug, which needs activation by cytochrome P450-3A4 (CYP3A4) to 4-hydroxyifosfamide, as shown in Fig. 1. Intracellular spontaneous decomposition of 4-hydroxyifosfamide yields the ultimate alkylating metabolite ifosforamide mustard [14]. Ifosfamide is deactivated to the noncytotoxic metabolites 2- and 3-dechloroethylifosfamide. Dechloroethylation yields an equimolar amount of chloroacetaldehyde, which is thought to be responsible for the neurotoxicity observed in about 10% of all patients receiving conventional single-agent dosing of ifosfamide [5]. Activation is mainly via CYP3A4 and

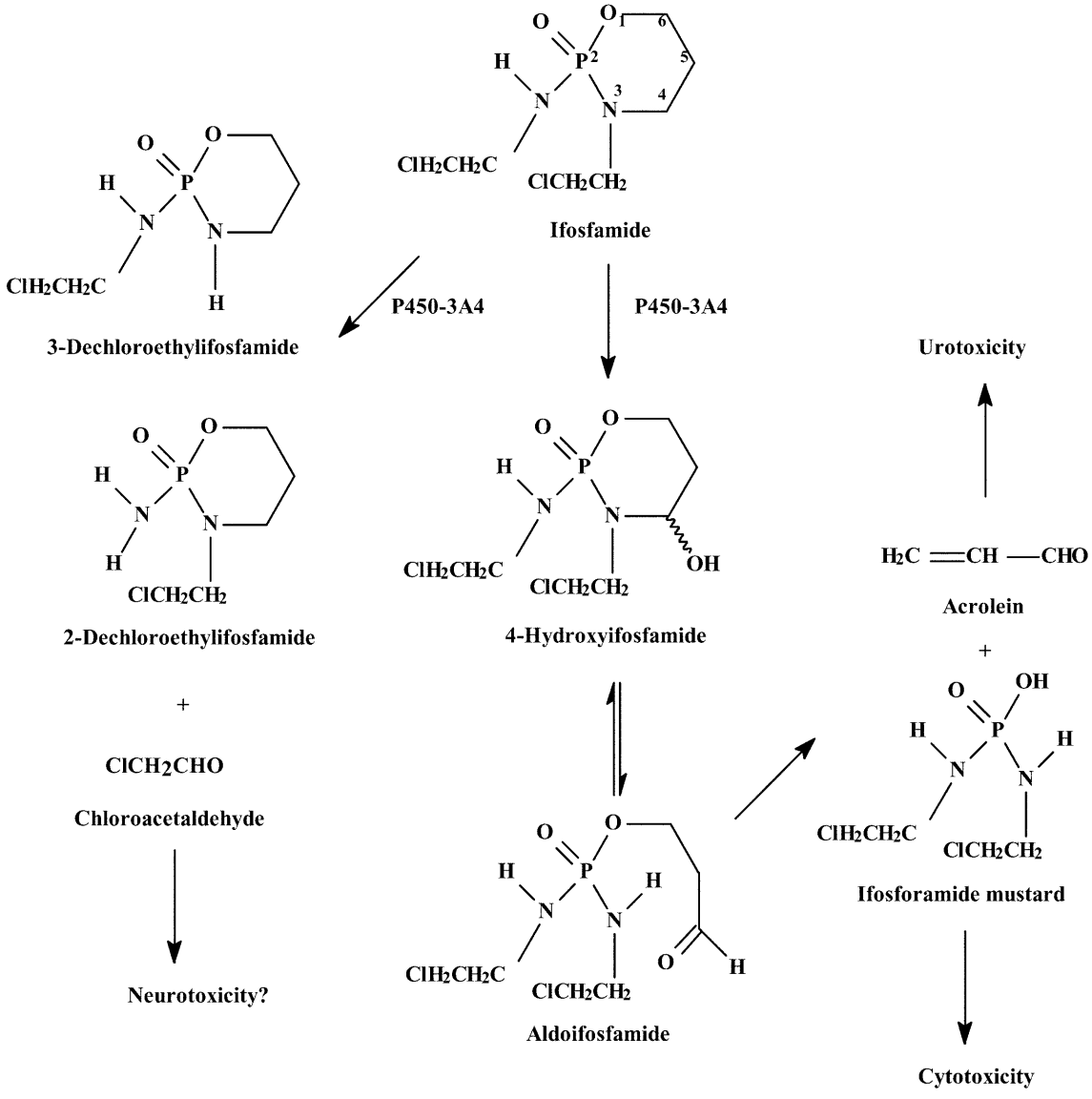

Fig. 1 Metabolism of ifosfamide

deactivation by CYP3A4 and possibly CYP2B6 [8]. Ifosfamide metabolism is subject to autoinduction, which will increase metabolism of ifosfamide with time [20].

In order to evaluate ifosfamide pharmacokinetics in relation to pharmacodynamic outcome, the pharmacokinetics of metabolites emerging from both the activation and deactivation routes need to be included in the evaluation. Historically, systemic exposure, particularly the area under the plasma concentration-time profile (AUC), is used in oncology in the development of these relationships [4, 7, 19]. Large interpatient variability in clinical toxicity is observed in ifosfamide treatment, which may be explained by variability in pharmacokinetics [23]. A population pharmacokinetic approach allows assessment of this variability.

In this study the pharmacokinetics of ifosfamide and its main metabolites were investigated in patients who participated in a phase I study of the combination ifosfamide, paclitaxel and carboplatin. The concentration-time profiles of ifosfamide were described using a recently developed population pharmacokinetic model [18]. Bayesian estimates obtained with this model were then used in the description of the concentration-time profiles of 2- and 3-dechloroethylifosfamide and 4-hydroxyifosfamide. The exposure to ifosfamide and its metabolites in four different ifosfamide treatment schedules was investigated. The urinary recoveries of ifosfamide and its metabolites were also determined.

Methods

Patients

Patients with resistant SCLC were hospitalized for administration of ifosfamide, paclitaxel and carboplatin in a phase I study. Inclusion criteria were: last chemotherapy given within 3 months, WHO performance status 1–2, white blood cell count $>3\times10^9$/l, platelets $>100\times10^9$/l and normal renal and liver function tests. Included in the study were 14 patients (9 males and 5 females) with

a mean age of 58 years (range 44–69 years), weight 76 kg (range 54–91 kg) and body surface area of 1.93 m^2 (range 1.54–2.10 m^2). The study protocol was approved by the Ethics Board of the University Hospital Groningen. Written informed consent was obtained from each patient before entering the study protocol.

Drug administration

Ifosfamide (Holoxan; ASTA Medica, Diemen) was delivered in vials containing dry powder and was dissolved in distilled water and administered as an intravenous (i.v.) infusion in glucose 5%. Hydration (total volume 2250 ml) was performed by means of the administration of the infusion solutions containing the three chemotherapeutic agents, without additional hydration steps. Paclitaxel (Taxol; Bristol-Myers Squibb, Woerden, The Netherlands) was delivered as a concentrated sterile solution, 6 mg/ml in 5-ml ampoules in polyoxyethylated castor oil (Cremophor EL) and dehydrated alcohol (1:1, v/v). Paclitaxel was diluted in a minimum volume of 250 ml and a maximum volume of 1000 ml of 5% dextrose or normal saline. Carboplatin (Paraplatin; Bristol-Myers Squibb) was supplied as a lyophilized product that contained 150 mg carboplatin and 150 mg mannitol as bulking agent. Immediately before use, the contents of each vial were reconstituted with 15 ml water for injection, and the total dose was added to 250 ml 5% dextrose. The dose of carboplatin in milligrams was calculated according to the formula: dose (mg) = carboplatin clearance (ml/min) × AUC (min·mg/ml). Carboplatin clearance was calculated according to the formula of Chatelut et al. [6].

Four different dose levels for ifosfamide were investigated in the phase I study. At the first dose level, sampling was performed in four patients receiving ifosfamide 1500 mg/m^2 on days 1 and 2 as a 1-h i.v. infusion. At the second dose level, four patients received ifosfamide 1000 mg/m^2 on days 1 and 2. At the third dose level, two patients received ifosfamide 2000 mg/m^2 on day 1 as a 1-h i.v. infusion. At the fourth dose level, four patients received ifosfamide 3000 mg/m^2 on day 1. At each dose level, after the last ifosfamide administration, paclitaxel 175 mg/m^2 was administered as a 3-h i.v. infusion and carboplatin at AUC 6 min·mg/ml as a 30-min i.v. infusion.

To prevent bladder toxicity, mesna (Uromitexan; ASTA Medica, Diemen) was administered in a total dose equal to the ifosfamide dose. Administration was partitioned equally over the i.v. infusion and twice orally 3 and 7 h thereafter. To avoid acute allergic reactions all patients received dexamethasone 8 mg orally every 12 h and 30 min before paclitaxel, clemastine 2 mg i.v. 30 min before paclitaxel and ranitidine 50 mg i.v. 30 min before paclitaxel. Antiemetics used were ondansetron twice daily for the first 3 days, and additionally dexamethasone and metoclopramide when needed.

Pharmacokinetic sampling

Pharmacokinetic sampling was performed during the first dosing cycle. The pharmacokinetic sampling at 0, 0.5, 1, 1.5, 2, 4, 8, 24, 24.5, 25, 25.5, 26, 28, 32 and 48 h after the start of the first ifosfamide infusion via an i.v. indwelling catheter was performed in patients receiving ifosfamide over 2 days (dose levels 1 and 2) and at 0, 1, 2, 5 and 24 h in patients receiving ifosfamide for 1 day (dose levels 3 and 4). First 2 ml whole blood was drawn and discarded, then 5 ml whole blood was collected into a lithium heparin-coated Vacutainer (Becton-Dickinson, Plymouth, UK) and placed on ice-water. The plasma was immediately separated by centrifugation at 1000 *g* for 5 min at 4°C. The plasma was aliquoted in three volumes of which two were precisely 1 ml. To these 1-ml volumes, 100 µl 2 *M* semicarbazide solution at pH 7.40 was added to stabilize the 4-hydroxyifosfamide. The remaining plasma was used for ifosfamide, and 2- and 3-dechloroethylifosfamide analysis. Furthermore, urine was collected for up to 24 h after the end of the last ifosfamide infusion and a representative sample of the collected urine was analysed for ifosfamide, and 2- and 3-dechloroethylifosfamide. Both plasma and urine samples were stored at –20°C for up to 1 month pending analysis.

Bioanalysis

Gas chromatography with selective nitrogen phosphorus detection was used for the determination of ifosfamide, and 2- and 3-dechloroethylifosfamide in urine and plasma [13]. Sample pretreatment consisted of alkalinized liquid-liquid extraction with ethyl acetate, transfer of the organic extract, evaporation to dryness and subsequent reconstitution in ethyl acetate. This method proved to be specific, sensitive, accurate (93.3–104.5%) and precise (< 5.5%) from 0.192 to 383 µ*M*, with a lower limit of quantification (LLQ) of 0.192 µ*M* for ifosfamide, and 2- and 3-dechloroethylifosfamide.

High-performance liquid chromatography (HPLC) was used for determination of 4-hydroxyifosfamide pharmacokinetics [17]. In brief, this method determined the 4-hydroxyifosfamide-semicarbazone derivative in plasma. The HPLC column used was reversed-phase C_8 with acetonitrile/0.025 *M* potassium dihydrogenphosphate (32:68 v/v) as mobile phase. Detection was performed at 230 nm. Sample pretreatment consisted of liquid-liquid extraction with ethyl acetate. This method was specific, sensitive, accurate (94.1–107.9%) and precise (< 7.2%) from 0.361 to 361 µ*M*, with a LLQ of 0.361 µ*M* 4-hydroxyifosfamide.

Data evaluation

Pharmacokinetic models were fitted to the data from l4 individuals using the population pharmacokinetic program NONMEM (Nonlinear Mixed Effects Modelling) [1, 3]. NONMEM estimates population parameters as typical parameter values with corresponding interindividual variability, usually as its SD, denoted as ω. This is accomplished by allowing each individual's data to be described by subject-specific pharmacokinetic parameters P_i. This parameter is assumed to come from the distribution of parameters in the population according to Eq. 1:

$$P_i = P_{pop} \times \exp(\eta_i) \quad (1)$$

where P_{pop} is the parameter value of a typical individual and η is the symmetrically distributed zero-mean variable with the SD denoted as ω.

For mixed effects models, the residual error corresponds to the difference between the observed concentration (C_{obs}) and predicted (C_{pred}) concentration by individual parameters (P_i). The residual or intraindividual error was described by a proportional and additive component according to Eq. 2:

$$C_{obs} = C_{pred} \times (1 + \varepsilon_1) + \varepsilon_2 \quad (2)$$

where ϵ_1 and ϵ_2 are zero-mean random variables with SDs σ_1 and σ_2. Either component of the residual error could be omitted if it did not provide an improvement in the fit of the data.

Model accuracy was evaluated using goodness-of-fit plots and precision of the parameter estimates. For the graphical goodness-of-fit analysis, extensive plotting was available through the use of Xpose [12], a purpose-built set of subroutines in S-PLUS (Mathsoft, 1997). For comparison between models the objective function value (which is minus 2 times the log likelihood) provided by NONMEM was used. For hierarchical models, the difference in objective function value is approximately χ-squared distributed, and formal testing between models can be performed, using the log-likelihood ratio test [1]. For non-hierarchical models, the objective function value cannot be used for formal testing, but we considered a difference of 9 units between models of the same number of parameters and identical databases, to indicate a real difference in description of the data [16].

The concentration-time profiles of ifosfamide were described using a recently developed population pharmacokinetic model as described by Eq. 3 [10, 18]:

$$\frac{dA_{ifo}}{dt} = R - \left(CL_{init} \times A_{enz} \times {}^{A_{ifo}}/_{V_{ifo}}\right) \quad (3)$$

where R ($\mu mol \cdot h^{-1}$) is the infusion rate of ifosfamide, CL_{init} ($l \cdot h^{-1}$) the initial ifosfamide clearance, A_{enz} the relative amount of enzyme in the hypothetical enzyme compartment and V_{ifo} (l) the volume of distribution. The concentration of ifosfamide C_{ifo} (μM) is the ratio of A_{ifo} and V_{ifo}. The change in A_{enz} over time in the enzyme compartment is dependent on C_{ifo} as follows:

$$\frac{dA_{enz}}{dt} = K_{enz,out} - K_{enz,out} \times A_{enz} \times \left(1 - \frac{C_{ifo}}{C_{ifo} + IC_{50}}\right) \quad (4)$$

where $K_{enz,out}$ (h^{-1}) is the first-order rate constant for enzyme degradation/inactivation and IC_{50} (μM) is the ifosfamide concentration at 50% of the maximum inhibition of enzyme degradation. The process of enzyme degradation depends on the amount of enzyme present and as such is best described as a first-order process. The induction half-life of the enzyme ($T_{1/2enz}$, h) was calculated as the ratio of ln(2) and $K_{enz,out}$ [18].

Bayesian estimates obtained with this model were then used in the description of the concentration-time profiles of 2- and 3-dechloroethylifosfamide and 4-hydroxyifosfamide. The change in the amount of a metabolite (A_m) over time could be described by Eq. 5:

$$\frac{dA_m}{dt} = \left(F_m \times CL_{(t)} \times \frac{A_{ifo}}{V_{ifo}}\right) - (K_m \times A_m) \quad (5)$$

where K_m (h^{-1}) is the elimination rate constant of the metabolite and F_m is the fraction of ifosfamide metabolized to the metabolite. The values of F_m and the volume of distribution of the metabolite (V_m, l) cannot be estimated separately in this model. Therefore, the ratio of F_m over V_m was estimated: F^* (l^{-1}). The ratio was used to calculate the area under the concentration-time curve (AUC_m) of the metabolite, as described by Eq. 6:

$$AUC_m = \frac{D}{K_m \times \frac{V_m}{F_m}} \quad (6)$$

where D (mol) is the ifosfamide dose administered to the patient.

The interindividual variability of each pharmacokinetic parameter was estimated using a proportional error model according to Eq. 1. The residual or intraindividual variability of ifosfamide and metabolite kinetics were described separately with a proportional and additive term according to Eq. 2. The Bayesian estimates of the AUCs of ifosfamide and its metabolites were obtained by describing the cumulative concentrations of these compounds over a given time. AUCs were obtained by extrapolation of ifosfamide and metabolite concentration-time profiles to 144 h after the start of the infusion, where concentrations were below the LLQ. The urinary excretions for ifosfamide and 2- and 3-dechloroethylifosfamide were calculated as the equimolar amount of the administered ifosfamide dose recovered in urine over 96 h.

Results

All 14 included patients were evaluable for plasma pharmacokinetics and 10 patients were evaluable for urine recovery measurements. The pharmacokinetic database consisted of 122 ifosfamide, 120 2-dechloroethylifosfamide, 122 3-dechloroethylifosfamide and 117 4-hydroxyifosfamide plasma concentrations. The observed ifosfamide and metabolite concentration-time profiles are shown in Fig. 2.

The pharmacokinetic parameters for ifosfamide are shown in Table 1. The relative error in the estimate of a population parameter is a measure of the precision of the estimation. These values were less than 35% which is considered good. For the parameters describing the increase in $CL_{(t)}$, such as $K_{enz,out}$ and IC_{50}, inclusion of interindividual variability did not improve the fit. This should not be interpreted as an absence of interindividual variability in these parameters, but only that the data did not contain sufficient information to estimate these [16]. Individual time profiles of the ifosfamide clearance over time ($CL_{(t)}$), are shown in Fig. 3.

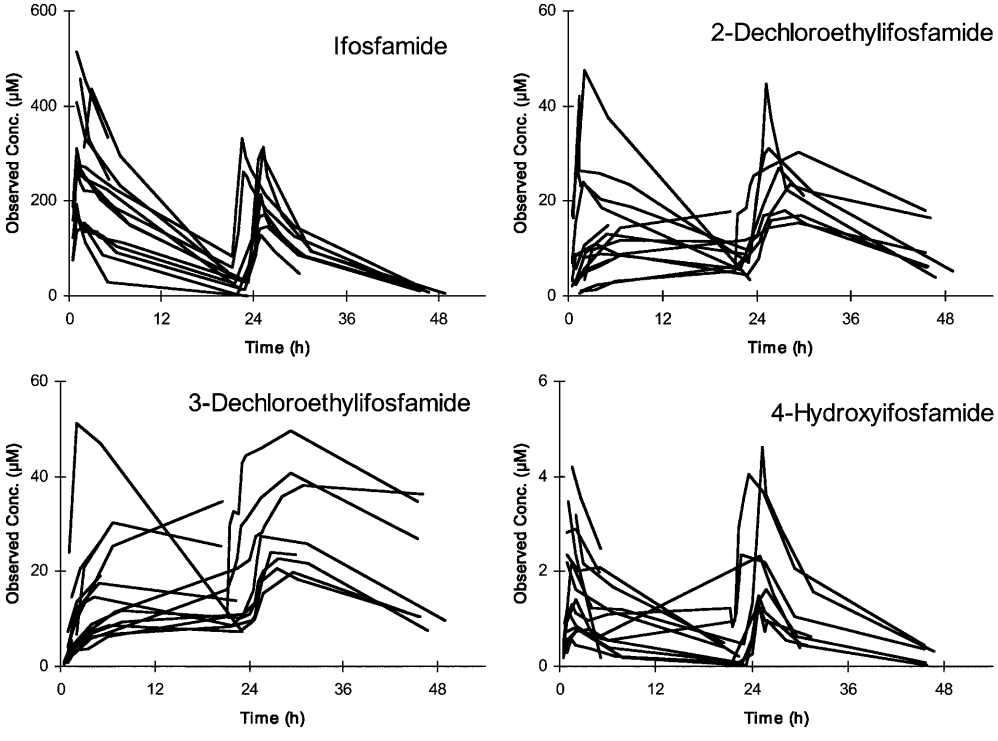

Fig. 2 Observed concentrations of ifosfamide and metabolites in 14 patients treated with four different schedules of ifosfamide followed by paclitaxel and carboplatin

Table 1 Estimates of pharmacokinetic population parameters for ifosfamide (IFO) with their relative standard error, interindividual variability and residual variability using an ifosfamide concentration-dependent description of the autoinduction (CL_{init} initial ifosfamide clearance, V_{ifo} volume of distribution of ifosfamide, $K_{enz,out}$ first-order rate constant for enzyme degradation, $T_{1/2,enz}$ induction half-life of the enzyme, IC_{50} ifosfamide concentration inhibiting 50% of the maximum inhibition of the enzyme degradation, *PE* proportional intraindividual error, *AE* additive intraindividual error)

Parameter	Mean estimate	Relative error (%)	Interindividual variability (%)
CL_{init} ($l \cdot h^{-1}$)	2.49	19	41
V_{ifo} (l)	46.2	6	17
$K_{enz,out}$ (h^{-1})	0.114	35	–
$T_{1/2,enz}$ (h)	6.1	–	–
IC_{50} (μM)	21.4	12	–
PE IFO (%)	17.4		
AE IFO (μM)	–		

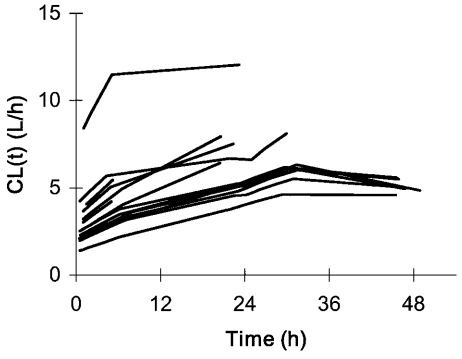

Fig. 3 Individual ifosfamide clearance-time ($CL_{(t)}$) profiles in 14 patients with an ifosfamide concentration-dependent increase in ifosfamide clearance. The profiles were obtained on the basis of the individual Bayesian parameter estimates provided by NONMEM

The population pharmacokinetic parameters of the metabolites are given in Table 2. The model predictions and individual Bayesian predictions versus observed ifosfamide and metabolite concentrations with their distribution around the line of identity are shown in Fig. 4. The accuracy of the estimates was reasonable (relative errors ranged from 14% to 66%). Modest interindividual variability was observed in the population parameters (29% to 52%).

The pharmacokinetic parameter estimates were used to estimate individual AUCs. Figure 5 illustrates the relationship between the systemic exposures of ifosfamide and metabolites and the absolute ifosfamide dose. A linear relationship was found for ifosfamide ($P < 0.001$) and 4-hydroxyifosfamide ($P = 0.003$), but not for 2-dechloroethylifosfamide ($P = 0.458$) or 3-dechloroethylifosfamide ($P = 0.065$). The urinary excretion of unchanged ifosfamide and its dechloroethylated metabolites are shown in Table 3. Fractionation of the dose over 2 days resulted in increased metabolite formation, especially of 2-dechloroethylifosfamide. The relationships between the urinary excretion of ifosfamide ($P = 0.238$) and the dechloroethylated metabolites

Table 2 Estimates of pharmacokinetic population parameters for 2-dechloroethylifosfamide (*2DCE*), 3-dechloroethylifosfamide (*3DCE*) and 4-hydroxyifosfamide (*4OHIF*) with their relative standard error, interindividual variability and residual variability (F^* ratio of the fraction of ifosfamide metabolized to the metabolite and the volume of distribution of the metabolite, *K* first-order elimination rate constant of metabolite, *PE* proportional residual error, *AE* additive residual error)

Parameter	Mean estimate	Relative error (%)	Interindividual variability (%)
F^*_{2DCE} (l^{-1})	0.0426	40	52
K_{2DCE} (h^{-1})	2.22	36	–
F^*_{3DCE} (l^{-1})	0.00771	14	36
K_{3DCE} (h^{-1})	0.138	16	47
F^*_{4OHIF} (l^{-1})	0.0180	60	–
K_{4OHIF} (h^{-1})	9.90	66	29
PE 2DCE	–		
AE 2DCE (μM)	6.89		
PE 3DCE (%)	33.1		
AE 3DCE (μM)	0.366		
PE 4OHIF (%)	30.5		
AE 4OHIF (μM)	0.218		

($P = 0.015$), and the absolute ifosfamide doses are shown in Fig. 6. Considerable interindividual variability was observed in the urinary recoveries.

Discussion

A recently developed population pharmacokinetic model was used to describe the concentration-time profiles of ifosfamide in patients treated with the combination ifosfamide, paclitaxel and carboplatin [18]. Description of the autoinduction of ifosfamide was done with a dynamic enzyme compartment linked to the ifosfamide concentration. This model allowed the clearance of ifosfamide to increase during infusion followed by a decline. The flexibility of this dynamic model is in accordance with the expected physiological mechanism of autoinduction [21]. Several other pharmacokinetic models were tested, such as the introduction of a peripheral compartment, a simple one-compartment model without autoinduction and a model with a time-dependent development of autoinduction according to Boddy et al. [2]. However, these models did not yield an increase in goodness-of-fit. In a population of 20 patients with soft tissue sarcomas receiving 9–12 g/m^2 over 72 h as a continuous infusion, similar values for the pharmacokinetic parameters of ifosfamide have been found [18]. Therefore, it can be concluded that the presented model accurately describes the fractionated dosing of ifosfamide as well as constant infusions.

Paclitaxel and carboplatin and their supportive care drugs were always administered after the last ifosfamide dose. Therefore, no influence of these drugs on the ifosfamide pharmacokinetics would be expected, nor have any interactions with ifosfamide been reported before.

The Bayesian estimates of the ifosfamide parameters were used in the modelling of the metabolite pharma-

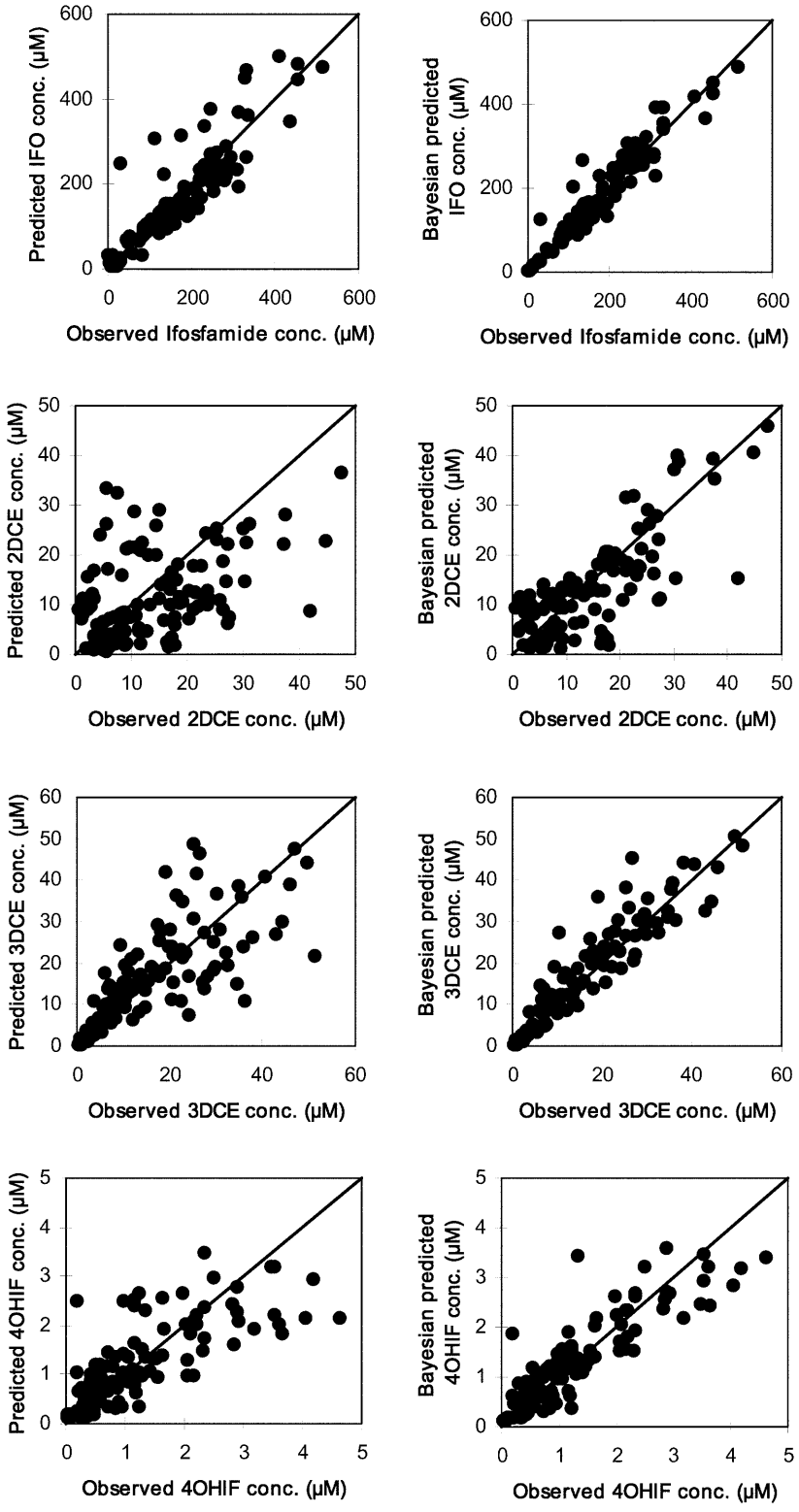

Fig. 4 The relationships between model predictions, individual Bayesian estimates and observed ifosfamide (*IFO*), 2-dechloroethylifosfamide (*2DCE*), 3-dechloroethylifosfamide (*3DCE*) and 4-hydroxyifosfamide (*4OHIF*) concentrations

cokinetics. The metabolite model adequately described the pharmacokinetics of the metabolites. The factor F^* (the ratio F_m over V_m) was determined. F_m will always be at least the urinary excretion (UE) of that metabolite and will not exceed 1 minus the urinary excretion of the other compounds (e.g. $UE_{3dce} < F_{3dce} < 1–UE_{2dce}–UE_{ifo}$). Therefore, the V_m (F_m/F^*) of 2- and 3-dechloroethylifosfamide will range between 0.6 and 20.3 l and 9.2 and 118 l, respectively. This is in accordance with the expectation that the metabolism of an exogenous compound such as ifosfamide (46.2 l) will lead to more hydrophilic compounds. The pharmacokinetics of

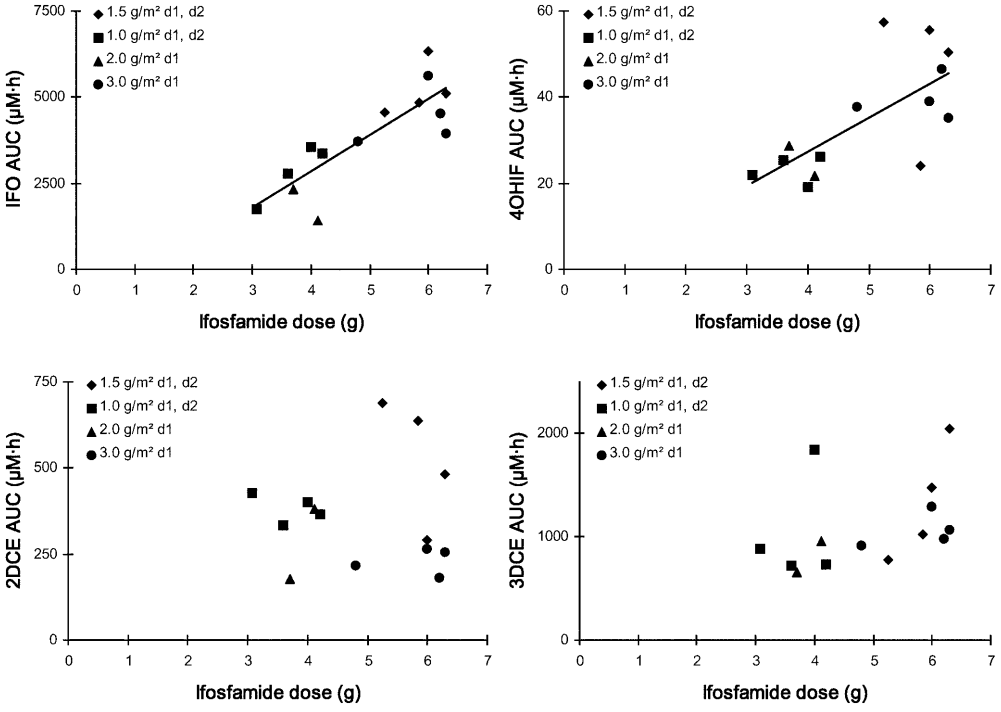

Fig. 5 The relationship between the systemic exposure to ifosfamide (*IFO*) and 2-dechloroethylifosfamide (*2DCE*), 3-dechloroethylifosfamide (*3DCE*) and 4-hydroxyifosfamide (*4OHIF*) in 14 patients after treatment with four different schedules of ifosfamide. Systemic exposure was based on the area under the plasma concentration-time curve (AUC)

Table 3 Percentage of dose excreted in the urine either unchanged as ifosfamide (*IFO*) or as metabolites 2-dechloroethylifosfamide (*2DCE*) or 3-dechloroethylifosfamide (*3DCE*) in ten patients

Patient no.	IFO dose (g)	IFO (%)	2DCE (%)	3DCE (%)	Total (%)
1	6.30	4.0	1.6	6.0	11.6
2	6.00	3.9	1.6	5.4	10.9
3	5.25	6.3	1.4	4.4	12.1
4	5.85	7.8	1.7	4.2	13.7
5	4.00	2.8	1.3	6.9	11.0
6	3.60	13.6	3.6	7.5	24.7
7	4.20	9.8	3.4	7.9	21.1
8	3.08	4.6	7.6	15.4	27.6
13	6.00	5.1	2.8	4.9	12.8
14	6.20	8.4	2.4	8.4	19.2
Mean ± SD		6.6 ± 3.3	2.7 ± 1.9	7.1 ± 3.3	16.5 ± 6.2

4-hydroxyifosfamide are formation rate-limited, as reflected in the high value for K_{4OHIF} compared to the formation of this metabolite. Therefore, it was more difficult to estimate K_{4OHIF}, causing a relatively high imprecision of the estimation.

Both ifosfamide and 4-hydroxyifosfamide exhibited a steeper dose-exposure relationship than dechloroethylated metabolites, as shown in Fig. 5. The lack of a distinct dose-exposure relationship of the dechloroethylated metabolites could be explained by the relatively high interindividual differences in exposure. Since the deactivation route, in contrast to the activation route, possibly occurs via both CYP3A4 and CYP2B6 more variability could be expected because there is evidence of interindividual variability in the expression of CYP2B6 [8]. Although, the four different treatment schedules of ifosfamide administration did not result in a

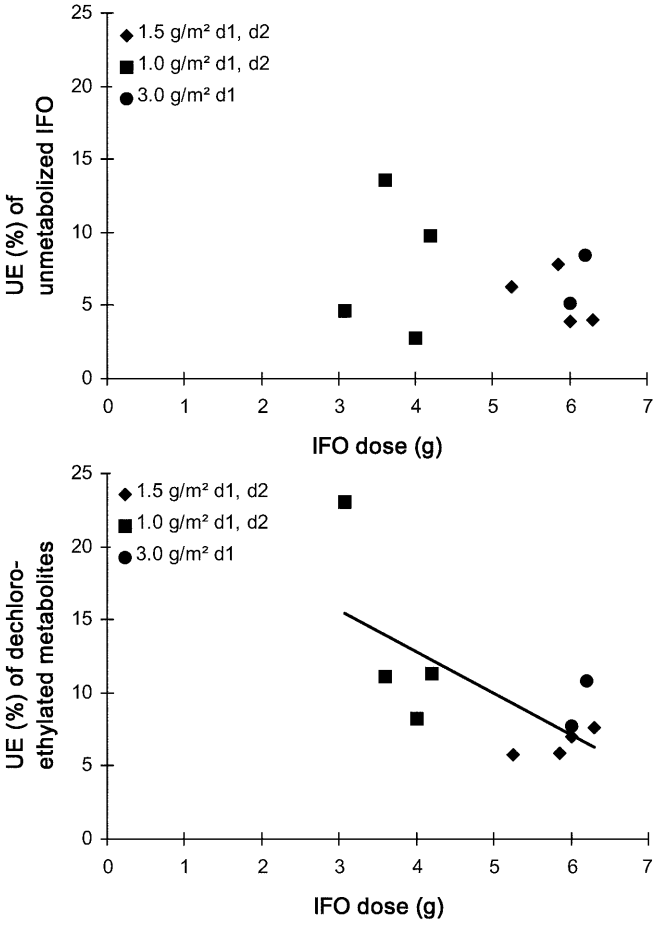

Fig. 6 Relationships between the urinary excretion (*UE*) of ifosfamide (*IFO*) and dechloroethylated metabolites and the absolute IFO dose in ten patients

wide dose range, some trends in the exposures due to dose fractionating could be observed. No trends in exposure to ifosfamide after administration of 3 g/m^2 ifosfamide given over 1 day compared with 2 days were observed. However, administration over 2 days resulted in higher metabolite formation. The AUC of 2-dechloroethylifosfamide in particular was increased after administration of ifosfamide over two consecutive days. This can be explained by autoinduction, resulting in increased metabolite formation. This trend was not observed with the activated metabolite 4-hydroxyifosfamide, exposure to which was not altered by fractionation of the ifosfamide dose over 2 days instead of 1 day. The clinical implications of these pharmacokinetic findings should be the subject of further investigation.

In one patient an increased CL_{init} was observed. This patient metabolized ifosfamide more rapidly than other individuals, but without an altered rate of autoinduction, which was reflected in elevated levels of dechloroethylated and hydroxylated metabolites. Although the ifosfamide and metabolite concentrations were lower and higher, respectively, in comparison with those of the other individuals, adequate individual Bayesian estimates were obtained (Fig. 3).

Urinary recovery of unchanged ifosfamide and its dechloroethylated metabolites was minor. As a result, dividing the ifosfamide clearance into an inducible metabolic clearance and a noninducible renal clearance also did not improve the goodness-of-fit of the model. Renal excretion of unchanged ifosfamide was $6.6 \pm 3.3\%$ and of the dechloroethylated metabolites $9.8 \pm 5.1\%$ of the administered dose. No clear trends in excretion after dose fractionation were observed. The urinary excretions are in accordance with previously reported data in patients receiving fractionated dosing of single-agent ifosfamide [14]. Previous stability studies have indicated no degradation of ifosfamide, or 2- and 3-dechloroethylifosfamide during a 24-h collection period [13]. However, degradation of 4-hydroxyifosfamide is too rapid to yield detectable levels in the urine [17].

The relationship between the ifosfamide dose and the percentage excreted as dechloroethylated metabolites (Fig. 6) was largely determined by patient no. 8 (Table 3). In this patient the second lowest dose-corrected exposure to ifosfamide was observed in combination with the highest and second highest dose-corrected exposure to 2- and 3-dechloroethylifosfamide, respectively. This was also reflected by the ifosfamide clearance value (approximately 8 l/h) in this patient, which was high in comparison with that in the other patients.

In conclusion, ifosfamide concentration-time profiles were adequately described by modelling the development of autoinduction with an ifosfamide concentration-dependent increase in ifosfamide clearance. Bayesian estimates of the pharmacokinetic parameters of ifosfamide were successfully used to describe the concentration-time profiles of 2- and 3-dechloroethylifosfamide and 4-hydroxyifosfamide. Systemic exposures to ifosfamide and its metabolites were calculated using Bayesian estimated pharmacokinetic parameters. Fractionation of the dose resulted in increased exposure of 2-dechloroethylifosfamide, probably due to increased autoinduction.

References

1. Beal SL, Boeckman AJ, Sheiner LW (1992) NONMEM Users Guide – part VI: PREDPP guide. NONMEM Project Group, University of California, San Francisco
2. Boddy AV, Cole M, Pearson DJ, Idle JR (1995) The kinetics of auto-induction of ifosfamide metabolism during continuous infusion. Cancer Chemother Pharmacol 36:53–60
3. Boeckman AJ, Sheiner LW, Beal SL (1994) NONMEM Users Guide – part V: introductory guide. NONMEM Project Group, University of California, San Francisco
4. Bongard DHJG van den, Mathôt RAA, Beijnen JH, Schellens JHM (2000) Pharmacokinetically guided dosing of chemotherapeutic agents. Clin Pharmacokinet 39:345-367
5. Cerny T, Küpfer A (1992) The enigma of ifosfamide encephalopathy. Ann Oncol 3:679–681
6. Chatelut E, Canal P, Brunner V, Chevreau C, Pujol A, Boneu A, Roché H, Houin G, Bugat R (1995) Prediction of carboplatin clearance from standard morphological and biological patient characteristics. J Natl Cancer Inst 87:573–580
7. Desoize B, Robert J (1994) Individual dose adaptation of anticancer drugs. Eur J Cancer 30:844–851
8. Ducharme MP, Bernstein ML, Granvil CP, Gehrcke B, Wainer IW (1997) Phenytoin-induced alteration in the N-dechloroethylation of ifosfamide stereoisomers. Cancer Chemother Pharmacol 40:531–553
9. Groen HJM, Fokkema E, Biesma B, Kwa B, van Putten JWG, Postmus PE, Smit EF (1999) Paclitaxel and carboplatin in the treatment of small-cell lung cancer patients resistant to cyclophosphamide, doxorubicin, and etoposide: a non-cross-resistant schedule. J Clin Oncol 17:927–932
10. Hassan M, Svensson USH, Ljungman P, Björkstrand B, Olsson H, Bielenstein M, Abdel-Rehim M, Nilsson C, Johansson M, Karlsson MO (1999) A mechanism-based pharmacokinetic-enzyme model for cyclophosphamide autoinduction in breast cancer patients. Br J Clin Pharmacol 48:669–677
11. Johnson DH, Einhorn LH, Birch R, et al (1987) A randomized comparison of high-dose versus standard-dose cyclophosphamide, doxorubicin and vincristine for extensive small-cell lung cancer. A phase III trial of the Southern Cancer Study Group. J Clin Oncol 11:1731–1738
12. Jonsson N, Karlsson M (1998) Xpose 2.0 User's manual, draft 4. Department of Pharmacy, Uppsala University, Sweden
13. Kaijser GP, Beijnen JH, Bult A, Wiese G, de Kraker J, Keizer HJ, Underberg WJM (1992) The determination of 2- and 3-dechloroethylifosfamide in plasma and urine. J Chromatogr 583:175–182
14. Kaijser GP, Beijnen JH, Bult A. Underberg WJM (1994) Ifosfamide metabolism and pharmacokinetics, a review. Anticancer Res 14:517–531
15. Kaijser GP, De Kraker J, Bult A, Underberg WJM, Beijnen JH (1998) Pharmacokinetics of ifosfamide and some metabolites in children. Anticancer Res 18:1941–1949
16. Karlsson MO, Molnar V, Freijs A, Nygren P, Bergh L, Larsson R (1999) Pharmacokinetic models for the saturable distribution of paclitaxel. Drug Metab Dispos 21:1220–1223
17. Kerbusch T, Huitema ADR, Kettenes-van den Bosch JJ, Keizer HJ, Ouwerkerk J, Beijnen JH (1998) High-performance liquid chromatographic determination of stabilized 4-hydroxyifosfamide in human plasma and erythrocytes. J Chromatogr B 716:275–284
18. Kerbusch T, Huitema ADR, Ouwerkerk J, Keizer HJ, Mathôt RAA, Beijnen JH (2000) Evaluation of the autoinduction of ifosfamide metabolism by a population pharmacokinetic approach using NONMEM. Br J Clin Pharmacol 49:555–561

19. Kobayashi K, Ratain MJ (1993) Individualizing dosing of cancer chemotherapy. Semin Oncol 20:30–42
20. Lewis LD, Fitzgerald DL, Harper PG, Rogers HJ (1990) Fractionated ifosfamide therapy produces a time-dependent increase in ifosfamide metabolism. Br J Clin Pharmacol 30:725–732
21. Park BK, Kitteringham NR, Pirmohamed M, Tucker GT (1996) Relevance of induction of human drug-metabolizing enzymes: pharmacological and toxicological implications. Br J Clin Pharmacol 41:477–491
22. Posner JB (1992) Management of brain metastases. Rev Neurol 148:477–487
23. Verweij J (1998) High-dose ifosfamide for soft tissue sarcomas: Set the scene, or senescence? Ann Oncol 9:807–809