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ORIGINAL ARTICLE

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Development of an optimal sampling strategy for clinical pharmacokinetic studies of the novel anthracycline disaccharide analogue MEN-10755

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Abstract *Aim*: MEN-10755 is a novel anthracycline analogue that has shown an improved therapeutic efficacy over doxorubicin in animal models, especially in gynaecological and lung cancers and is currently under clinical development for the treatment of solid tumours. The aim of the project was to develop an optimal sampling strategy for MEN-10755 to provide an efficient basis for future pharmacokinetic/pharmacodynamic investigations. *Methods*: Data from 24 patients who participated in a phase I clinical pharmacokinetic study of MEN-10755 administered as a short i.v. infusion were included. Individual pharmacokinetic values were calculated by fitting the plasma concentration data to a two-compartment model using nonlinear least-squared regression (KINFIT, Ed 3.5). Population pharmacokinetic analysis was carried out using (a) the traditional standard two-stage method (STS) based on all data (KINFIT-ALL), (b) the iterative two-stage Bayesian (IT_2B) population modelling algorithm (KINPOP), and (c) the STS method using KINFIT and using four optimally timed plasma concentrations (KINFIT-OSS4). Determinant (D) optimal sampling strategy (OSS) was used to evaluate the four most information-rich sampling times. The pharmacokinetic parameters V_c (l), k_{el} (h^{-1}), k_{12} (h^{-1}) and k_{21} (h^{-1}) calculated using KINPOP served as a model for calculation of four D-optimal sampling times. D-optimal sampling data sets were analysed using KINFIT-OSS4 and compared with the population model obtained by the traditional standard two-stage approach for all data sets (KINFIT-ALL). *Results*: The optimal sampling times were: the end of the infusion, and 1.5 h, 3.8 h and 24 h after the start of the infusion. The four-point D-optimal sampling design determined in this study gave individual parameter estimates close to the basic standard estimates using the full data set. *Conclusion*: Because accurate estimates of pharmacokinetic parameters were achieved, the four-point D-optimal sampling design may be very useful in future studies with MEN-10755.

Keywords Optimal sampling strategy · Pharmacokinetics · Anthracycline · MEN-10755

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Introduction

The anthracycline antibiotics, the most representative of which is doxorubicin, are frequently used chemotherapeutic agents with well-established clinical efficacy in many different human cancers [17, 42]. Myelotoxicity

and cardiotoxicity as well as the development of multidrug resistance limit their use in clinical practice. Over the past 30 years, there have been efforts to develop new derivatives with improved curative properties, reduced toxicity and less drug resistance [42]. During the course of synthesis and biological evaluation of new third generation anthracyclines, MEN-10755 has been identified as a promising compound, based essentially on the hypothesis that elongation of the carbohydrate moiety and its variation might result in improved compounds. In preclinical studies the novel anthracycline MEN-10755 appeared to have an improved therapeutic efficacy over doxorubicin, especially in gynaecological and lung cancers [2, 29].

Two phase I tolerability and pharmacokinetic studies with different dosing schedules of MEN-10755 have been performed in patients with refractory malignancies [3, 34]. Like other anthracyclines, haematological toxicity is dose-limiting. The pharmacokinetics were found to be linear in both studies, and the $AUC_{0-\infty}$ (which represents the average plasma exposure to drug) was found to be proportional to the administered dose and the administered dose to be related to (dose-limiting haematological) toxicity. No active metabolites of MEN-10755 have been found. The 3-weekly regimen of MEN-10755 has been selected for further phase II clinical studies in patients with advanced or metastatic ovarian cancer, in non-small-lung carcinoma and in soft tissue sarcoma.

Knowledge of the relationship between pharmacokinetic and pharmacodynamic parameters of a new potential drug is of importance in optimization of drug dosage, i.e. the dosage that will give the maximum likelihood of a therapeutic response whilst minimizing the risk of unnecessary or unacceptable toxic side effects [4, 16, 24, 31]. This is particularly important with respect to cytotoxic drug therapy, where the therapeutic window is narrow. Antineoplastic drugs represent a class of compounds showing a narrow therapeutic index. Determination of the area under the concentration versus time curve (AUC) has proven to be of value in predicting the clinical response and toxicity of several anticancer agents [5, 13, 21, 24, 27, 28, 33, 39, 40]. Other pharmacokinetic parameters, such as the maximum concentration, the steady-state concentration and the time above a 'threshold' concentration, have also been shown to be related to toxicity and efficacy [7, 14, 15, 33].

With traditional pharmacokinetic analysis many postinfusion plasma samples (e.g. 10–12 samples) are required to adequately describe individual parameters such as the AUC. These designs are clinically inconvenient, laborious, expensive and patient-unfriendly. A more efficient strategy for the estimation of individual patient pharmacokinetic parameters, with reduced cost and less disturbance to the patient, is the application of limited-sampling techniques [40].

By using a limited sample strategy, an accurate estimate of pharmacokinetic parameters of a drug in individual patients can be made using plasma samples collected at a limited number of time points. Different methods for limited-sampling strategies for anticancer agents have been proposed [13, 22, 25, 26, 32, 36, 38, 40]. The most commonly employed approach to estimate the AUC for the selection of sampling times is a forward stepwise regression procedure, defined as the limited-sampling model [22, 40]. In this approach the sampling time-point that best predicts the AUC is chosen first. The second point selected is that which provides the most additional information. Another approach uses D-optimal sampling theory which has the major advantage of allowing estimation of model parameters other than the AUC [40]. This approach has been shown to perform well for the anthracycline doxorubicin [23, 32].

The aim of this study was to develop a D-optimal sampling strategy for MEN-10755 in order to provide a cost-effective basis for future pharmacokinetic-pharmacodynamic investigations, which might have the potential to lead to dosing strategies based on the characteristics of the individual subject. By using this optimal sampling strategy (OSS), the pharmacokinetic parameters predicting antitumor effects in further (phase II) studies will be determined with four informative postinfusion concentration-time points, while minimizing inconvenience, effort and cost.

Patients and methods

Patient population

Data from 24 out of 37 patients (see pharmacokinetic methods section) who participated in a phase I dose-finding study of MEN-10755 performed at the University Hospital of Copenhagen in Denmark and at The Norwegian Radium Hospital in Oslo were analysed. In this study, patients received MEN-10755 as a short intravenous infusion every 3 weeks at doses ranging from 4 to 110 mg/m^2 [3]. All patients had a histologically or cytologically confirmed diagnosis of a solid tumour not amenable to established forms of treatment.

Blood sampling and analytical method

Blood samples were collected just before, and 10, 15, 20, 25, 30, 45 min and 1, 2, 4, 6, 9, 12, 24, 36 and 48 h after the start of the infusion. Blood samples were immediately centrifuged to separate the plasma, frozen and stored at −20°C until analysis by a validated high-performance liquid chromatographic (HPLC) method. The analytical method used has been described previously [3]. The lower limit of quantitation (LLQ) was 0.5 μg/l in human plasma. The plasma absolute recovery was 79.5%. The intra- and interassay variabilities (precision) expressed as coefficient of variation (%) were less than 2.3% in the concentration range 10 to 100 μg/l, whereas

the intra- and interassay variabilities for the 0.5 μg/L (the LLQ of plasma) were 2.7% and 3.2%, respectively. The accuracy evaluated at the same concentrations and expressed as relative error (%) ranged from −2.9% to 5.7%.

Plasma MEN-10755 concentration data were available from 32 patients.

Pharmacokinetic methods

There were 24 data sets with sufficient and accurate time versus drug concentration records available for the analysis. The following pharmacokinetic parameter estimates were used to compare model parameters estimated using all data points with those obtained using the four OSS: the AUC (h·μg/l/dose) calculated using the linear trapezoidal method, total body clearance (CL, l/h/m^2), volume of distribution of the central compartment (V_c, l/kg), elimination rate constant from the central compartment ($k_{el} = k_{10}$, h^{-1}), and the intercompartmental rate constants (k_{12} and k_{21}, h^{-1}).

Individual pharmacokinetic analysis

The KINFIT module of the MW\PHARM computer program (MediWare, ed 3.5; Groningen, The Netherlands) using nonlinear least-squares regression was used to calculate the individual pharmacokinetic parameter estimates [30]. The postinfusion kinetics of MEN-10755 could be described by both a two- and a three-compartment model. Model discrimination was based on Akaike's information criterion (AIC) [1]. For simplicity, individual pharmacokinetic parameter estimates were calculated by fitting the plasma concentration data to the two-compartment model. These calculated parameter estimates were considered the best possible estimates and were used as the standard against which parameters obtained with the OSS were compared. For the AUC, the trapezoidal method was preferred, because this method reflects more exactly the "real measured" concentration. In order to weight each plasma concentration correctly by the reciprocal of its variance (Fisher information index), the standard deviation (SD) was determined over the working range [19]. The SD of the observation varied linearly with the plasma concentration (C) according to the following equation: $SD = 0.047554 \times C$. This equation for the assay error was incorporated into the appropriate sections of the ADAPT II program to compute D-optimal times [10].

Optimal sampling strategy

The determinant (D) optimal sampling design (OSS) [20] was used to evaluate the most information-rich sampling times. Optimal sampling times were determined as described by Vinks et al. [41] with a version of the SAMPLE module (Courtesy of R.W. Jelliffe, Los Angeles, Calif.) of the ADAPT II package of programs of D'Argenio and Schumitzky [8, 10]. Sampling times were constrained to be between the end of the infusion and 24 h. The SAMPLE program calculated for each set of pharmacokinetic parameters the most informative sampling times. With a two-compartment model, the pharmacokinetic parameters V_c (l), k_{el} (h^{-1}), k_{12} (h^{-1}) and k_{21} (h^{-1}) were used for the calculation of four D-optimal times. D-optimal sampling times were calculated in a sequential manner [9, 11, 41]. For a first set of D-optimal times, the individual pharmacokinetic parameter estimates of a randomly selected patient, calculated by Bayesian estimation with the last version of the MW\PHARM program were used. The next subject's parameter estimates were calculated by Bayesian estimation using data closest to the calculated D-optimal times for the first patient. The means of the thus-obtained parameter estimates of all previous patients were subsequently used to calculate a new set of optimal times for the next patient. This procedure was repeated until a stable set of optimal times for all patients was calculated.

Pharmacokinetic evaluation and statistical analysis

The STS was used as the traditional method for pharmacokinetic analysis [37]. In the first stage, the individual parameters were estimated by nonlinear least squares fitting employing all data (KINFIT-ALL). Next, as the second stage parameter estimates for all patients were summarized as means and SDs.

As an alternative approach for pharmacokinetic analysis, an iterative two-stage Bayesian (IT_2B) population modelling algorithm (KINPOP; MediWare, Groningen, The Netherlands) was used [30], also employing all data (IT_2B-ALL). The iterative two-stage analysis uses a Bayesian algorithm to refine individual estimates and the population model recursively until means and covariances are stable. Parameter estimates obtained with Bayesian fitting usually predict plasma concentrations better (with greater precision) than those obtained by non-Bayesian nonlinear regression [18]. Both pharmacokinetic approaches (KINFIT and IT_2B) were also employed using four optimally timed plasma concentrations (KINFIT-OSS4 and IT_2B-OSS4, respectively).

The parameter estimates obtained with the full data set analysed by IT_2B (KINPOP-ALL) and the sparse D-optimal sampling data sets analysed with KINFIT (KINFIT-OSS4) and KINPOP (IT_2B-OSS4) were compared with the population model obtained with the standard two-stage approach (KINFIT-ALL). The percent mean error (%ME), computed as a measure of bias, and the mean absolute error (%MAE), used as a measure of precision, were calculated as follows [41]:

$$\textit{bias} \qquad \%ME = \frac{100}{n}\sum \frac{X_i - KINFIT_i}{KINFIT_i}$$

$$\textit{precision} \qquad \%MAE = \frac{100}{n}\sum \frac{|X_i - KINFIT_i|}{KINFIT_i}$$

where n is the number of subjects ($n = 24$), X_i is either a pharmacokinetic parameter estimate for the ith subject calculated using D-optimal times and the STS method employing KINFIT (KINFIT-OSS4) or a pharmacokinetic parameter estimate for the ith subject calculated using the full data set and the iterative two-stage Bayesian estimator. $KINFIT_i$ is the parameter estimate and basic standard for the ith subject with the nonlinear least-square estimator (i refers to patients 1 to 24).

The relationship between the calculated pharmacokinetic parameter estimates (AUC, CL and V_c) obtained with the D-optimal design (KINFIT-OSS4) and those obtained with full data sets (KINFIT-ALL) were also evaluated by regression analysis (coefficient of determination, R^2). The model with the lowest bias (%ME + standard error (SE%)), the highest correlation coefficient, and the most convenient sampling method was considered the optimal model [40, 41].

The relative performance of the KINFIT-OSS4 and the KINFIT-ALL prediction models was evaluated according to the method described by Sheiner and Beal [35]. The bias of a model was determined as the mean prediction error (ME), which is the mean difference between the measured and predicted concentrations. The precision was calculated as the mean squared prediction error (MSE), which is equal to the mean of the sum of squared differences between the actual and predicted concentrations. The root mean squared prediction error is equal to the square root of MSE and was used to convert the measure back into concentration units [40].

To determine the relative precision of the models, the difference in MSEs was computed [35]:

Relative precision $\quad \Delta\,\mathrm{MSE} = \mathrm{MSE}_1 - \mathrm{MSE}_2$

where $M(S)E_1$ is the M(S)E of the first model and $M(S)E_2$ that of the second. The significance of the relative precision of models was then evaluated by calculating whether the confidence intervals included zero (i.e. no difference in performance between the two models). The Wilcoxon signed rank test was used to test the differences between the STS-derived AUC estimates and the AUC values using the KINFIT-OSS4 strategy.

Results

Individual pharmacokinetic analysis

Data from 24 patients were analysed. The patient characteristics are summarized in Table 1. The 24 patients received different dosages ranging from 8 to 220 mg (4–110 mg/m^2). The calculated pharmacokinetic parameter estimates are listed in Table 2. The pharmacokinetics (C_{max} and AUC) of MEN-10755 were linear in the range of doses used (4–110 mg/m^2) [3]. The data were well-described by a two-compartment model for all patients (AIC) [1]. Distribution volumes (V, V_c and V_{ss}) and clearance (CL) were significantly related to body size expressed as weight in kilograms and body surface area in meters squared, respectively. The AUC of each patient was normalized to the individual administered dosage in milligrams.

Table 1 Demographic and clinical data of 24 patients (17 male, 7 female) available for pharmacokinetic analysis

Characteristic	Mean ± SD
Age (years)	52.8 ± 6.9
Height (cm)	178.5 ± 7.5
Weight (kg)	72.6 ± 12.5
Doses (mg)	116.6 ± 70.1
BSA (m^2)[a]	1.9 ± 0.2
CL_{CR}(ml/min/1.73 m^2)[b]	90.7 ± 22.0

[a]Body surface area, calculated by the method of Du Bois and Du Bois [12]
[b]Creatinine clearance, calculated according to the formula of Cockcroft and Gault [6]

Table 2 Population pharmacokinetic parameter estimates after a single intravenous dose ranging from 8 to 220 mg for 24 patients using a nonlinear least-squares estimator and STS analysis

Symbol, parameter (unit)	Mean ± SD
$t_{1/2\alpha}$, distribution half-life (h)	0.39 ± 0.08
$t_{1/2\beta}$, elimination half-life (h)	14.99 ± 3.58
V, volume of distribution (l/kg)	3.04 ± 0.76
V_c, V of central compartment (l/kg)	0.19 ± 0.07
V_{ss},V at steady-state (l/kg)	1.82 ± 0.48
CL, total body clearance (l/h/m^2)	5.42 ± 1.23
$AUC_{(0-\infty)}$, area under the curve (h·µg/l/mg)[a]	105.38 ± 28.66

[a]Calculated using the trapezoidal method

Optimal sampling strategy (OSS)

The means ± SD of the final four D-optimal sampling times were: $t_{(1)}$ = end of the infusion, $t_{(2)} = 1.49 \pm 0.06$ h, $t_{(3)} = 3.81 \pm 0.16$ h and $t_{(4)} = 24$ h after the start of the infusion. Concentrations sampled at times closest to the selected time points, namely the end of the infusion, and 4.0 h and 24 h, respectively, were used for correlation analysis. Because no sample was taken at t = 1.49 h, the plasma MEN-10755 concentrations at 1.49 h were estimated from the plasma concentration-time curve, using the mean concentration at t = 1.49 h in KINFIT-ALL.

Pharmacokinetic parameter estimates based on OSS

The results of the four population pharmacokinetic analyses are presented in Table 3. The mean parameter estimates obtained with the traditional STS method based on KINFIT-ALL data were used as the basic standard. The mean parameter estimates obtained by the other three methods were compared with this standard. Table 3 shows that parameter estimates calculated by the iterative two-stage Bayesian algorithm

Table 3 Pharmacokinetic parameter estimates for MEN-10755 determined for 24 patients as estimated by non-linear regression (KINFIT) and IT_2B estimator (*CL* total body clearance, V_c volume of distribution of central compartment, k_{el} elimination rate constant from central compartment, k_{12} and k_{21} intercompartmental rate constants, $AUC_{(t-\infty)}$ area under the curve). Values are means ± SD

Method[a]	CL ($l/h/m^2$)	V_c (l/kg)	k_{el} (h^{-1})	k_{12} (h^{-1})	k_{21} (h^{-1})	$AUC_{(t-\infty)}$ (h·μg/l/mg)
KINFIT-ALL	5.42 ± 1.23	0.19 ± 0.07	0.79 ± 0.20	0.99 ± 0.23	0.11 ± 0.02	105.38 ± 28.66
KINPOP-ALL	5.50 ± 1.42	0.20 ± 0.09	0.76 ± 0.25	0.97 ± 0.31	0.11 ± 0.02	
Bias[b]	1.53	7.42	−3.35	−2.53	−0.91	
Precision[c]	1.53	7.42	3.35	2.53	0.91	
KINFIT-0SS4	5.10 ± 1.12	0.14 ± 0.05	1.04 ± 0.27	1.14 ± 0.23	0.15 ± 0.02	131.04 ± 33.35
Bias[b]	−5.51	31.42	−25.70	16.73	39.76	25.43
Precision[c]	6.69	31.89	25.70	17.18	39.76	25.43
KINPOP-OSS4	4.79 ± 1.15	0.13 ± 0.04	1.06 ± 0.25	1.14 ± 0.19	0.15 ± 0.01	
Bias[b]	−11.61	−32.37	33.73	15.57	37.27	
Precision[c]	11.61	32.37	33.73	15.57	37.27	

[a]KINFIT-ALL, weighted nonlinear least-squares fitting of all available data; KINPOP-ALL, iterative Bayesian population fitting with all available data; KINFIT-OSS4, weighted nonlinear least-squares fitting with four optimally determined concentrations; KINPOP-OSS4, iterative Bayesian population fitting with four optimally determined concentrations;
[b]Bias, mean percent error (%ME)
[c]Precision, mean absolute percent error (%MAE)

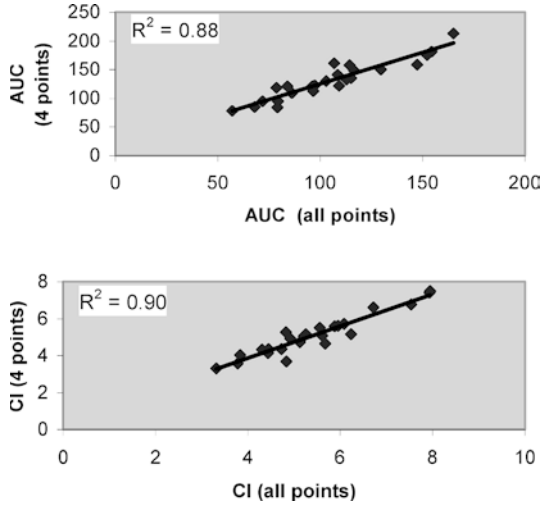

Fig. 1 Relationships between the estimates of AUC (h·μg/l/dose) and CL ($l/h/m^2$) obtained with KINFIT based on all available data (KINFIT-ALL) and the estimates with four D-optimally sampled concentrations (KINFIT-OSS4). The R^2 values for AUC and CL are 0.88 and 0.90, respectively

(KINPOP-ALL) were unbiased and precise. It is also clear (see Table 3) that on average, the parameter estimates obtained by KINFIT-OSS4 agreed well with those of KINPOP-OSS4. Both population models based on the four OSS samples differed slightly from the STS estimates.

The four-sampling-derived estimates for individual patients (KINFIT-OSS4) were highly correlated with parameters based on KINFIT-ALL data, as shown in Fig. 1. The important parameters for predicting an anthracycline analogue concentration after infusion (AUC and CL) showed excellent correlation ($R^2 = 0.88$ and $R^2 = 0.90$, respectively). V_c and the distribution parameter k_{12} showed a high correlation ($R^2 = 0.72$ and $R^2 = 0.80$, respectively) and performed well in describing individual concentration-time courses; k_{21} showed more scatter ($R^2 = 0.14$).

The AUC, calculated using the trapezoidal method, was significantly higher using the KINFIT-OSS4 strategy than that derived using the STS (Wilcoxon signed rank test, $Z = -4.286$, $P < 0.001$). The AUC for the KINFIT-OSS4 strategy was overestimated by 25.4% compared to the STS-derived AUC.

The relative predictive performance of the KINFIT-OSS4 compared to the KINFIT-ALL prediction model was evaluated by calculating the relative precision of the models. Although the mean squared error of the KINFIT-ALL model was smaller to that of the KINFIT-OSS4 model (MSE = 0.152 versus MSE = 0.747, respectively), there was no significant difference in performance of precision between the two models (ratio = 0.595), as the confidence interval included zero (CI = −5.887, 5.292).

Discussion

In order to describe the relationship between drug exposure and drug effect, determination of the concentration-time course of a drug is of particular importance. Traditionally, accurate determination of pharmacokinetic profiles required collection of many, typically ten or more, postinfusion blood samples. The drawing and processing of these samples is inconvenient for the patient, time-consuming and expensive. The merging of an optimal sampling design and population pharmacokinetic analysis has been shown to be a useful and cost-effective alternative [40].

The purpose of this study was to evaluate data-sparse techniques to model and predict the pharmacokinetics of a novel anticancer agent, MEN-10755. D-optimal sampling design was used with data from a phase I study of MEN-10755. Full- and sparse-data pharmacokinetic modelling was performed with the STS method and an

IT_2B algorithm. Individual pharmacokinetic parameter estimates obtained with the IT_2B method (KINPOP-ALL) agreed very well with those obtained with the traditional nonlinear least-squares estimator (KINFIT-ALL, basic standard; Table 3). The four-point D-optimal sampling design in this study gave individual parameters estimates close to the standard estimates using the full data set (Fig. 1 and Table 3).

More importantly, the OSS provided parameter estimates that showed good concordance with those obtained from all available data, allowing good prediction of the AUC, CL and V_c, relevant parameters for individualized MEN-10755 dosing. It can be concluded that only four time-points; t = end of the infusion, and 1.5, 3.8 and 24 h after infusion are necessary to characterize MEN-10755 disposition. The distribution between the central and peripheral compartments was less well correlated with the basic standard as could be expected due to little information in the data time points. However, this did not negatively influence the prediction of the AUC. The AUC predicted by the KINFIT-OSS4 strategy was overestimated by 25.4% compared to the STS-derived AUC. This is important to know, since AUC is a measure of total drug exposure and a major determinant of clinical response and toxicity of several anticancer agents [5, 13, 21, 24, 27, 28, 33, 39, 40].

For future phase II studies, the times for sample collection can now be set. Application of this design will give the necessary clinical flexibility as slight deviations in sampling time and infusion duration can be allowed for. Large deviations from the planned sampling times would affect the precision of the prediction and, therefore, should be avoided.

In conclusion, the application of the D-optimal sampling strategy with nonlinear regression or IT_2B techniques would facilitate pharmacokinetic modelling and improve feasibility of pharmacokinetic-pharmacodynamic studies in patients treated for cancer. Not only the costs of the determination of the drug levels, but also the inconvenience for both the patients and the medical staff would be greatly reduced in future studies by using an adaptive optimal sampling model.

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