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ORIGINAL ARTICLE

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Population pharmacokinetics of oxaliplatin

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Abstract The objective of this study was to explore correlations between a variety of covariates and oxaliplatin ultrafilterable and blood pharmacokinetic parameters. Data from 40 patients receiving oxaliplatin combined with 5-fluorouracil and levofolinic acid as standard treatment for advanced colorectal cancer were analysed. Plasma ultrafilterable, blood, and urine platinum concentrations were determined by flameless atomic absorption spectrophotometry. Data were analysed according to a population pharmacokinetic method using the NONMEM program. The best fit for oxaliplatin plasma ultrafilterable clearance (CL) was given by the following equation, which considers four covariates: body surface area (BSA, in metres squared), age (in years), sex (0 if male, 1 if female), and serum creatinine (Scr, in micromoles per liter): CL (l/h) = 5.49x BSA + 4.55xBSAx(140–AGE)x(1–0.15xSEX)/Scr. By taking into account these covariates, the interindividual variability in CL decreased from 43% to 33%. Renal clearance represented 34% of the overall elimination. This value was obtained by recovering urine over only 5 h from the beginning of the infusion and modelling the data using NONMEM. We would recommend the use of this methodology for pharmacokinetic studies in oncology in which renal clearances of the drug are presently rarely explored. The oxaliplatin blood concentrations versus time observed during the three-cycle period were well-described by a three-compartment model with first-order elimination from the central compartment. No significant intrapatient pharmacokinetic variability was observed between cycles. The relationship we obtained using the population approach between oxaliplatin CL and covariates may allow rational reduction of oxaliplatin dose in cases of elevated serum creatinine levels.

Keywords Oxaliplatin · Population pharmacokinetics · Renal clearance · Colorectal cancer

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Introduction

Oxaliplatin is the first available diaminocyclohexane (DACH) platinum compound. The drug presents a spectrum of antitumour activity that does not overlap with that of cisplatin or carboplatin [6]. Oxaliplatin is currently approved for the treatment of metastatic colorectal cancer in combination with fluorouracil and folinic acid [4]. The main dose-limiting toxicities of oxaliplatin are haematological suppression and peripheral sensory neuropathy [5]. The latter toxicity is also cumulative. The ultrafilterable fraction is rapidly cleared from plasma by covalent binding to tissues (including to plasma proteins and erythrocytes) and renal elimination [7]. Oxaliplatin undergoes rapid and nonenzymatic biotransformation leading to monochloro-, dichloro- or diaquo-DACH that can react with DNA. Unlike cisplatin and carboplatin, there are only a limited number of pharmacokinetic studies concerning oxaliplatin. So far, renal impairment has been identified as the only factor showing interindividual variability. Massari et al. [12] observed a correlation between the clearance of ultrafilterable oxaliplatin and that of creatinine. The objective of this study was to explore, using a population pharmacokinetic method using NONMEM, correlations between a variety of covariates and oxaliplatin ultrafilterable and blood pharmacokinetic parameters. Data from 40 patients receiving oxaliplatin combined with 5-fluorouracil (5FU) and levofolinic acid (FA) as standard treatment for advanced colorectal cancer were analysed. Intrapatient variabilities were also studied since data after the three first cycles were available for some patients.

Patients and methods

Patients

The characteristics of the 40 patients (from 29 to 82 years of age, 22 males and 18 females) are shown in Table 1. Patients received oxaliplatin in combination with 5FU and FA as standard treatment for advanced colorectal cancer. Three protocols were successively studied. For all three protocols, oxaliplatin was administered according to a 3-h i.v. infusion (day 1) followed by FA and 5FU (days 1 and 2). The oxaliplatin dose and intercycle period differed between protocols: 130 mg/m^2 every 3 weeks (17 patients), 80 mg/m^2 every 2 weeks (12 patients), or 100 mg/m^2 every 2 weeks (11 patients). For the first two protocols, the daily dose was 250 mg FA, and 1500 mg/m^2 5FU. For the third protocol, each day FA (200 mg/m^2, 2-h i.v. infusion) was followed by a 5FU bolus (400 mg/m^2) and then a 22-h infusion of 5FU (400 mg/m^2). The local ethics committee approved the protocol and informed written consent was obtained from each patient.

Sampling and platinum analysis

Blood samples (5 ml) were collected at 1.5, 3, 3.25, 3.5, 4, 5, 8 and 24 h after the beginning of the 3-h oxaliplatin infusion. One fraction (1 ml) of blood was directly frozen for later determination of blood concentrations (nanograms of platinum expressed as oxaliplatin per millilitre of blood). The other fraction was immediately centrifuged at 4°C, and the plasma was separated and ultrafiltered using an Amicon MPS1 micropartition system with YMT membranes (30,000 MW cut-off) at 4°C. Urine samples were collected from time 0 to 5 h after the beginning of the oxaliplatin administration. Plasma ultrafilterable, blood, and urine samples were kept at 20°C until flameless atomic absorption spectrophotometric analysis according to a previously described method [9]. The limit of quantification was 10 ng/ml for plasma ultrafiltrate and urine, and 25 ng/ml for blood.

Pharmacokinetic analysis

Data were analysed according to a population pharmacokinetic method using the NONMEM program [3] (version V, level 1.1, running on a Pentium 200 pro). Two separate analyses were conducted. The first included both plasma ultrafilterable and urine oxaliplatin concentrations. All data (from cycle 1 to cycle 3 for the three oxaliplatin dosages 80, 100, and 130 mg/m^2) were considered with the exception of the plasma ultrafilterable concentrations at 24 h after the oxaliplatin infusion (this late sample mainly comprised platinum conjugates to ultrafilterable amino acids, i.e. fraction likely inactive). The second analysis included the blood concentrations from time 0 (beginning of the first infusion) to 24 h after the third infusion (for the three oxaliplatin dosages 80, 100, and 130 mg/m^2). For both analyses, a proportional error model was used for interpatient and residual variabilities. The influences of the following covariates on oxaliplatin clearances (both plasma ultrafilterable and blood clearance, CL) were examined: age, sex, body weight, height, body surface area (BSA, calculated according to the Dubois formula), serum creatinine (Scr), creatinine clearance (calculated according to the Cockcroft-Gault equation), proteinaemia, and haemoglobinaemia. In analysing the data, NONMEM computed the value of a statistical function, the minimal value of the objective function, which is equal to minus twice the log likelihood. For testing the covariates, the different models were compared using an approximation to the chi-squared distribution of the objective function value of the reduced model minus that of the full model. The number of degrees of freedom is equal to the difference in the number of parameters between two nested models.

Table 1 Characteristics of the 40 patients studied. Values are means (range),except numbers of males/females

Sex (male/female)	22/18	
Age (years)	59	29–82
Body weight (kg)	65	45–96
Height (cm)	165	148–179
Body surface area (m^2)[a]	1.71	1.40–2.09
Plasma creatinine (μmol/l)	83	39–153
Creatinine clearance (ml/min)[b]	78	28–135
Proteinaemia (g/l)	71	57–80
Haemoglobinaemia (g/102 ml)	12.0	8.4–16.9

[a]Calculated according to the Duboisformula
[b]Calculated according to theCockcroft-Gault equation

Results

Plasma ultrafilterable and urine concentrations

Data were available for all 40 patients, 34 patients, and 21 patients in cycles 1, 2, and 3, respectively. Ultrafilterable platinum was not detectable in the samples obtained just before infusion in cycle 2 and cycle 3, showing that free oxaliplatin did not accumulate throughout the treatment. The oxaliplatin plasma ultrafilterable concentrations versus time were well-described by a two-compartment model with first-order elimination from the central compartment (Fig. 1). Residual variability was 24%. The intraindividual variabilities in CL between cycles were evaluated using the interoccasion variability as described by Karlsson and Sheiner [8]. Table 2 shows the mean pharmacokinetic parameters, their interindividual variabilities, and the percentage change in oxaliplatin CL between cycles. The best fit for oxaliplatin plasma ultrafilterable CL was given by the following equation, which considers four covariates: BSA (in metres squared), age (in years), sex (0 if male, 1 if female), and Scr (in micromoles):

$$\mathrm{CL(L/hr)} = \theta 1 \times \mathrm{BSA} + \theta 2 \times \mathrm{BSA} \times (140 - \mathrm{AGE}) \times (1 - 0.15 \times \mathrm{SEX})/\mathrm{Scr}$$

with mean values (±95% confidence interval) for coefficients: $\theta 1 = 5.49 \pm 2.86$ (l/h per m^2); $\theta 2 = 4.55 \pm 3.14$ (l/h per m^2 x μM). By taking into account these covariates, the interindividual variability in CL decreased from 43% to 33%. Deletion of each of these covariates from the equations was associated with a significant increase in the objective function. In the covariate equation for CL, the influence of age and sex corresponds to those described for estimation of the creatinine clearance using the Cockcroft-Gault equation; alternative values did not significantly improve the objective function. Preliminary analysis showed significant differences between ultrafilterable oxaliplatin clearances depending upon the regimen: a lower clearance was observed after administration of 85 mg/m^2 than after 130 mg/m^2. However, since covariates (such as age and Scr) were taken into account, this difference did not persist, showing that differences in the patients' characteristics between

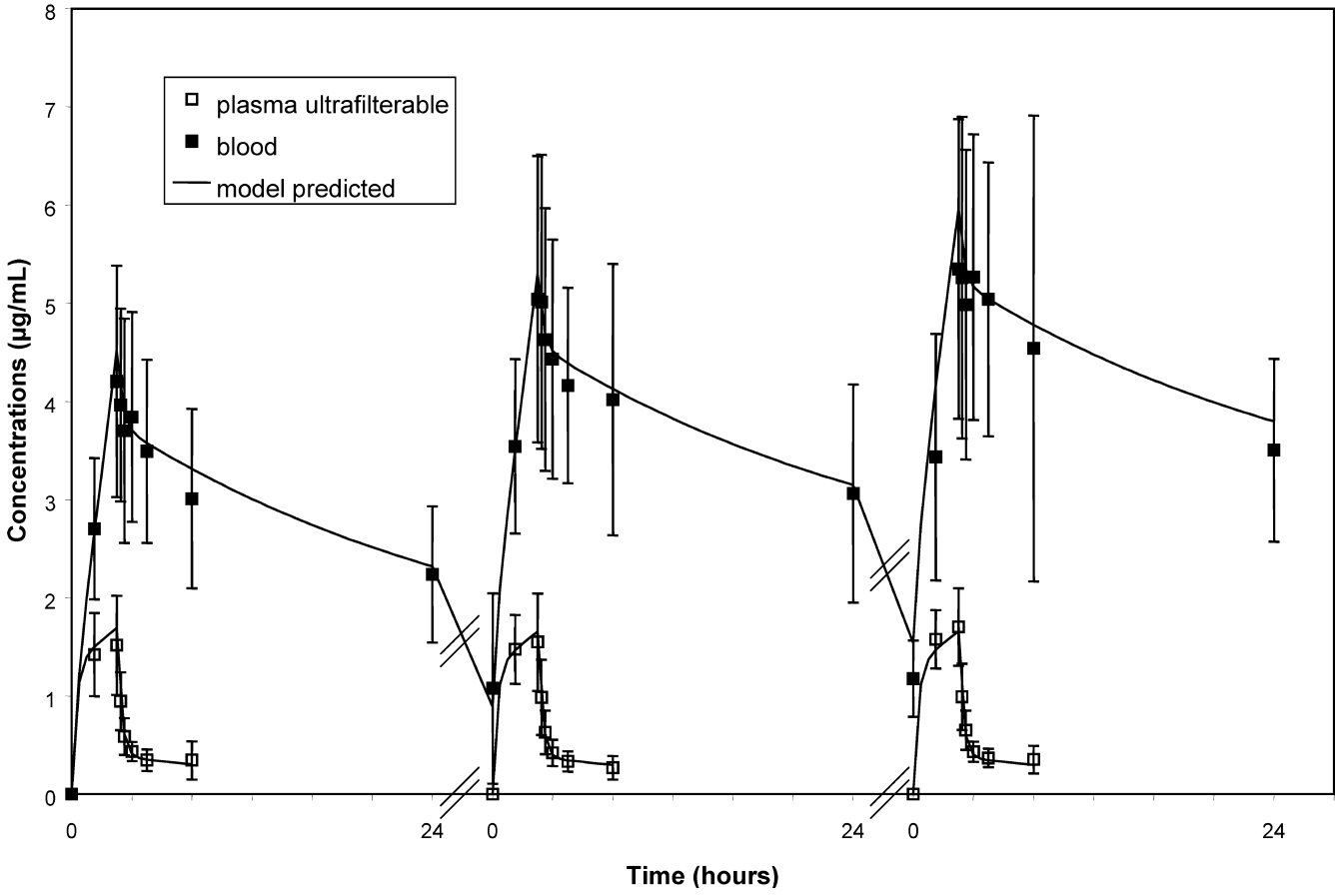

Fig. 1 Mean observed oxaliplatin concentrations (±SD) and predicted concentrations according to the mean pharmacokinetic parameters of patients ($n=20$) treated with 130 mg/m^2 of oxaliplatin every 3 weeks

Table 2 Mean ultrafilterable oxaliplatin pharmacokinetic parameters (*CV* coefficient of variation, *CI* confidence interval, *NE* evaluable)

Parameter	Mean	Interpatient variability (%CV)
Clearance (l/h)		
Cycle 1 ($n=40$)	18.7	43
Cycle 2 ($n=34$)	17.7	
Change versus cycle 1 (%)	–1% (95% CI ± 11%)	
Cycle 3 ($n=21$)	16.5	
Change versus cycle 1 (%)	–14% (95% CI ± 8%)	
Central volume of distribution (l)	40.8	43
Peripheral volume of distribution (l)	21.0	NE
Urinary elimination (%)	34.3	35

groups were involved rather than nonlinear pharmacokinetics with dose.

The renal clearance represented 34.3% of the total clearance (corresponding to the plasma ultrafilterable concentrations) on average with an interindividual variability of 35%.

Table 3 Mean blood oxaliplatin pharmacokinetic parameters (*CV* coefficient of variation, $K_{12}K_{21}K_{13}K_{31}$ transfer rate constants between central volume and peripheral volumes of distribution, *NE* not evaluable)

Parameter	Mean	Interpatient variability (%CV)
Clearance (l/h)	0.127	50
Central volume of distribution (l)	17.9	25
K_{12} (h^{-1})	2.97	NE
K_{21} (h^{-1})	1.77	NE
K_{13} (h^{-1})	0.0747	NE
K_{31} (h^{-1})	0.0119	36

Blood concentrations

Significant accumulation of oxaliplatin was observed throughout the treatment (Fig. 1). The oxaliplatin blood concentrations versus time were well-described by a three-compartment model with first-order elimination from the central compartment. No interoccasion variability was used. Residual variability was 19% with a similar quality of fit between cycles. Mean pharmacokinetic parameters are shown in Table 3. CL was significantly correlated with covariates according to the following equation, which considers two covariates:

BSA (in metres squared), and haemoglobinaemia (Hb, g/100ml):

$$CL(L/hr) = \theta 1 \times BSA \times (1 - \theta 2 \times Hb)$$

with mean values (±95% confidence interval) for coefficients: $\theta 1 = 0.28 \pm 0.07$ (l/h per m^2); $\theta 2 = 0.058 \pm 0.006$ (100 ml/g). By taking into account these covariates, the interindividual variability in CL decreased from 50% to 32%. Deletion of each of these covariates from the equations was associated with a significant increase in the objective function.

Toxicity

In order to assess the relationship between pharmacokinetic parameters and occurrence of peripheral neuropathy, we performed a prospective clinical evaluation of neuralgic symptoms in all patients. A total of 245 courses of chemotherapy were administered during this study, with an average of 6.1 courses per patient. After the first two courses, nine patients (22.5%) experienced grade 1 or 2 acute neuropathy. After four courses of the oxaliplatin-containing regimen, 19 patients out of 31 experienced grade 1 or 2 acute neuropathy. Only 6 patients (out of 15 receiving eight or more courses) had grade 1 cumulative sensory neuropathy, which never occurred before the eighth course.

A correlation study was then retrospectively performed to search for clinical or biological (including pharmacokinetic parameters such as AUC and maximum concentrations after cycle 1) predictive factors. Haemoglobin levels, total protein levels and pharmacokinetic data could not be correlated with the occurrence of neuropathy.

In the same way, in order to assess the relationship between haematological toxicity and pharmacokinetic data, we performed a retrospective analysis of all haematological data. The very low rate of haematological toxicity after the first cycle or later did not allow any correlation to be observed. For example, only one patient experienced grade 3 neutropenia and only one patient grade 3 thrombocytopenia after the first cycle.

Discussion

Only a few clinical pharmacokinetic studies oxaliplatin have been conducted. Moreover, they have all included a limited number of patients (never more than 20). A population approach has never been applied to this drug. The present results for plasma ultrafilterable oxaliplatin are consistent with those previously reported. In the literature, the mean values for ultrafilterable oxaliplatin CL range between 9.34 and 25.7 l/h [10]. We obtained a mean value (18.7 l/h) close to the higher end of this range. The discrepancy between studies is likely due to differences between sampling protocols. For example, a value of 13.3 l/h associated with a long terminal half-life (27.3 h) has been obtained by taking into account concentrations 24 h after oxaliplatin administration. However, by 24 h after administration, platinum is almost entirely conjugated to low molecular weight amino acids. Since this form is probably not clinically relevant, we chose to retain only the data from the 8 h following the beginning of the infusion. Moreover, it should be noted that our analysis was based on the measurement of a mixture of platinum species since oxaliplatin is rapidly converted to other platinum compounds (such as dichloro-, monochloro-, and diaquo-DACH platin) [1].

The interindividual variability was limited in comparison with that of other cytotoxic compounds such as carboplatin. This may have been due to the fact that renal clearance represented only 34% of the overall elimination. We obtained this value by recovering urine only during the 5 h after the beginning of the infusion and modelling the data using NONMEM. Using a conventional method (48-h urine recovery after administration), Graham et al. and Marty obtained similar values (33 and 36%, respectively), and Allen et al., and Misset and Allain obtained larger values (54 and 57%) when more extensive recoveries were performed (i.e. at 120 h and 264 h, respectively) [2, 7, 13]. The methodology we used based on a limited urine recovery time has the advantage that the risk of loss of urine is decreased. We would recommend the use of this methodology for pharmacokinetic studies in oncology in which renal clearances of the drug are presently rarely explored.

Since ultrafilterable oxaliplatin is partly eliminated by the kidneys, it is understandable that renal function is one of the covariates to which ultrafilterable oxaliplatin CL was correlated. Massari et al. have previously found a correlation between creatinine clearance and that of ultrafilterable oxaliplatin [12]. The relationship we obtained using a population approach between oxaliplatin CL and covariates may allow a rational reduction in oxaliplatin dose in cases of elevated serum creatinine levels. Renal impairment is not a usual characteristic of patients with colorectal cancer, but this compound has been evaluated in the treatment of other tumours such as ovarian cancer [11]. The results of the present pharmacokinetic study would be useful for oxaliplatin dosing in these patients who frequently have poor renal function. A "typical" female patient (57 years old, BSA 1.56 m^2) with a serum creatinine level of 131 μmol/l (80% greater than the mean observed value in females) would have an ultrafilterable oxaliplatin CL 20% lower. In the same way, a reduction in oxaliplatin dosage would be recommended in elderly patients, since age has been found to be a significant covariate. It is also interesting to note that BSA is a covariate significantly correlated with ultrafilterable oxaliplatin CL, justifying consideration of this morphological parameter for calculation of dose.

Moreover, blood oxaliplatin CL was also proportional to BSA. Haemoglobinaemia was the second significant covariate for blood CL with a negative

relationship between them. This may be explained by the binding of oxaliplatin in erythrocytes. However, erythrocyte-associated platinum is not considered to be a reservoir of pharmacologically active platinum due to the irreversible nature of the binding. Therefore, we do not recommend the use of the relationship between haemoglobinaemia and blood oxaliplatin CL for oxaliplatin dosing. The intrapatient pharmacokinetic variability was low. The percentage change in ultrafilterable CL between cycle 1 and cycle 2 was not significant. CL tended to decrease from cycle 1 to cycle 3 (i.e. mean value –14%), but the value was not clinically significant. Although accumulation in the blood was observed, no change in the blood pharmacokinetic parameters was apparent since the data (i.e. blood concentrations versus time) were well-fitted with constant parameters during the first three cycles of treatment.

We developed models for both ultrafilterable and blood oxaliplatin concentrations, which accurately described the data (i.e. two- and three-compartment model, respectively). These models could be used in future clinical pharmacokinetic studies to estimate individual pharmacokinetic parameters of oxaliplatin using the Bayesian approach with limited individual data. Indeed, although its interindividual variability is limited, oxaliplatin pharmacokinetics have still to be studied in specific population such as elderly patients. For example, we have already used this Bayesian approach to perform drug monitoring of oxaliplatin given to a patient with complete cholestatic syndrome. We have analysed two available ultrafilterable plasma levels (i.e. at time 0, and 2.5 h after the end of a 3-hour infusion) and the urine concentration corresponding to the 5.5-h period after the beginning of the infusion. The individual CL was 15.4 l/h (with a renal clearance corresponding to 43% of the total elimination), indicating no particular pharmacokinetic behaviour of oxaliplatin in this patient. Moreover, evaluation of potential pharmacokinetic interactions between oxaliplatin and other antitumour drugs will be required when combinations are developed. With these considerations in mind, we place our database and corresponding models at the disposal of other investigators.

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