Population pharmacokinetics of oxaliplatin in patients with metastatic cancer

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Our aim was to develop a population pharmacokinetic model of ultrafilterable oxaliplatin in metastatic cancer patients. Oxaliplatin was administered by 2- or 4-h infusions, 50, 65, 75, 85, 100 or 130 mg/m^2 to 56 patients. Blood samples were collected over 28 h. Plasma concentrations of ultrafilterable oxaliplatin were determined by flameless atomic absorption spectrophotometry. Population pharmacokinetic analysis was performed using a non-linear mixed-effects modeling method. Ultrafilterable oxaliplatin concentration–time profiles showed a secondary peak or a shoulder aspect post-infusion, attributed to the existence of an enterohepatic recirculation (EHR). They were best described by a two-compartment model incorporating an EHR component. Plasma clearance (CL) was related positively to body weight (BW) and negatively to serum creatinine (SCr), and was greater in male patients than in female patients. This covariate modeling resulted in a decrease in the interindividual variability for CL from 104 to 62%. The central distribution volume (V_1) and inter-compartmental clearance (Q) were related to BW. Typical population estimates of CL, central distribution volume (V_1), input rate constant into gallbladder (k_{1B}) and lag time for drug reabsorption (T_{LAG}) were 14.1 or 8.5 l/h (male or female patients), 24.9 l, 1.8 h^{-1} and 2.0 h, respectively. The final pharmacokinetic model was validated using 200 bootstrap samples of the original data. We conclude that a two-compartment with EHR model adequately described ultrafilterable oxaliplatin pharmacokinetics, explaining a secondary transient increase in concentration. This study identified combined-covariate-effects ultrafilterable oxaliplatin clearance, supporting dose adjustment of oxaliplatin based on BW, gender and corrected for SCr level, if drug exposure is thought to be related to therapeutic or toxic issues. *Anti-Cancer Drugs* 14:817–824

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Introduction

Oxaliplatin is a recent platinum coordination complex widely used in the treatment of metastatic colorectal cancer in combination with fluoropyrimidines, including tumors resistant to cisplatin. When compared to other platinum derivatives, oxaliplatin lacks the nephrotoxicity of cisplatin and myelosuppressive effect of carboplatin, but it produces reversible peripheral neuropathy [1]. The pharmacokinetic profile of ultrafilterable oxaliplatin has been investigated via classical pharmacokinetic approaches [2] and was generally described by a three-compartment open model, although a two-compartment model was also used, with terminal half-lives ranging from 23 to 269 h, including a recent study [3]. Moreover, these studies, generally performed on a limited number of patients, failed to provide clear relationships between oxaliplatin pharmacokinetics and patient characteristics, and thus did not support a model for an *a priori* individualized drug dose regimen.

Pharmacokinetics of drugs have generally been shown to be heterogeneous in cancer patients due to both clinical status and concomitant multiple drug intake, leading to an increased toxicity (increased drug exposure) or a lower efficacy (decreased drug exposure). Thus the investigation of interpatient and intrapatient variabilities has become an important issue in the pharmacokinetic studies as recommended by regulatory agencies [4].

The aim of the present study was to analyze previously acquired data during two clinical trials by using a population pharmacokinetic approach. Only one of these clinical trial data has already been published [5]. A second goal was to assess the influence of patient characteristics on ultrafilterable oxaliplatin pharmacokinetics, in order to propose an *a priori* dosing strategy for this drug.

Methods

Patients and treatment

Patients were entered in a phase I trial with oxaliplatin administered alone and in a phase I–II trial where oxaliplatin was given in combination with folinic acid/5-fluorouracil/irinotecan. For each protocol, written

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informed consent of patient and ethics committee approval were obtained before the beginning of the treatment. Eligibility criteria included: patients with histologically proven metastatic cancer, objectively measurable and/or evaluable disease; age ≥ 18 years, WHO performance status of 0–2, adequate hematological parameters (granulocytes $\geq 2.0 \times 10^9$/l; platelets $\geq 100 \times 10^9$/l). Oxaliplatin was given as 2- or 4-h i.v. infusions, 50, 65, 75, 85, 100 or 130 mg/m^2.

For each patient, the demographics and baseline laboratory values were recorded. Body surface area (BSA) and Cockroft–Gault index (CGI) were calculated according to usual formulae [6,7].

Analytical method

Plasma concentrations of ultrafilterable oxaliplatin were determined by flameless atomic absorption spectrophotometry, as previously described [5].

Population pharmacokinetic modeling

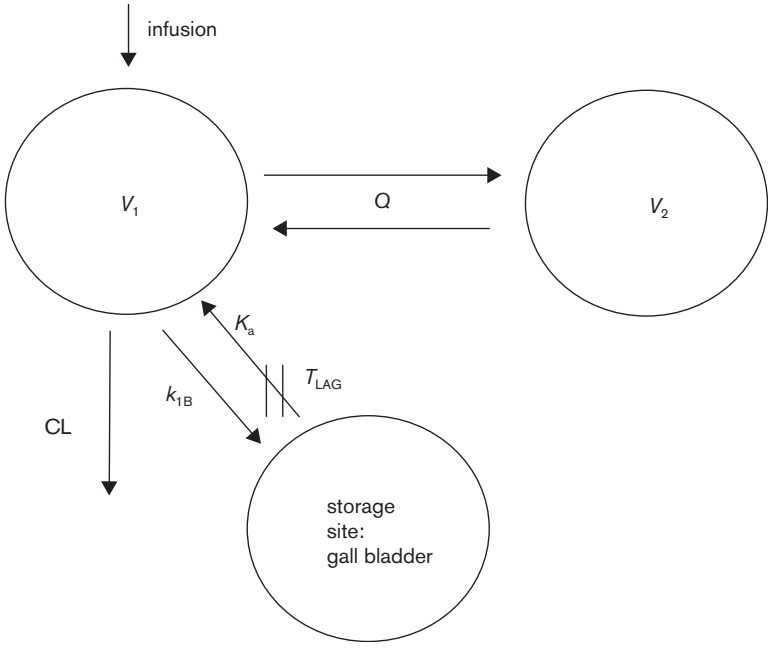
Concentration–time data were analyzed using a nonlinear mixed effects modeling approach, using the MP2 programs [8]. Oxaliplatin data was analyzed according to a two-compartment pharmacokinetic model including an elimination/storage component (Fig. 1). The release from the storage site (likely the gallbladder) is assumed to occur as a bolus at the time of expulsion from the gallbladder, T_{LAG}. The other parameters of the final structural model were plasma CL and Q (elimination and intercompartmental clearances), V_1 and V_2 (central and peripheral compartment volumes), k_{1B} (excretion rate constant from compartment 1 to storage site), and K_a (absorption rate constant from the storage site). The integrated equations of the model have already been detailed [9].

Several error models were investigated (i.e. proportional error model with constant coefficient of variation and additive random effects model) to describe interpatient and residual variability. An extensive graphical analysis of predicted versus observed (PRED versus OBS) concentrations was performed to test the value of each model ($\text{PRED} = b^*\text{OBS} + Y_0$, the regression parameters estimates b and Y_0 should be as close as possible to 1 and 0). Comparison between the means of the individual Bayesian (i.e. POSTHOC) parameter estimates and the population estimates was also used to discriminate between the error models (the 95% confidence intervals of POSTHOC mean estimates should include the mean population estimates).

The influence of each patient covariate on pharmacokinetic parameters was systematically tested via a generalized modeling according to the following equation, using CL for example:

$$\text{CL} = \text{TV(CL)} * \{\text{BW}/\text{median(BM)}\}^{\theta\text{BW}}$$

Fig. 1



Scheme of the EHR model used for the population pharmacokinetic analysis. V_1 and V_2, central and peripheral distribution volumes; CL and Q, elimination and intercompartmental clearances; k_{1B}, excretion rate constant from compartment 1 to storage site (gallbladder); T_{LAG}, time of drug expulsion from gallbladder; K_a, absorption rate constant.

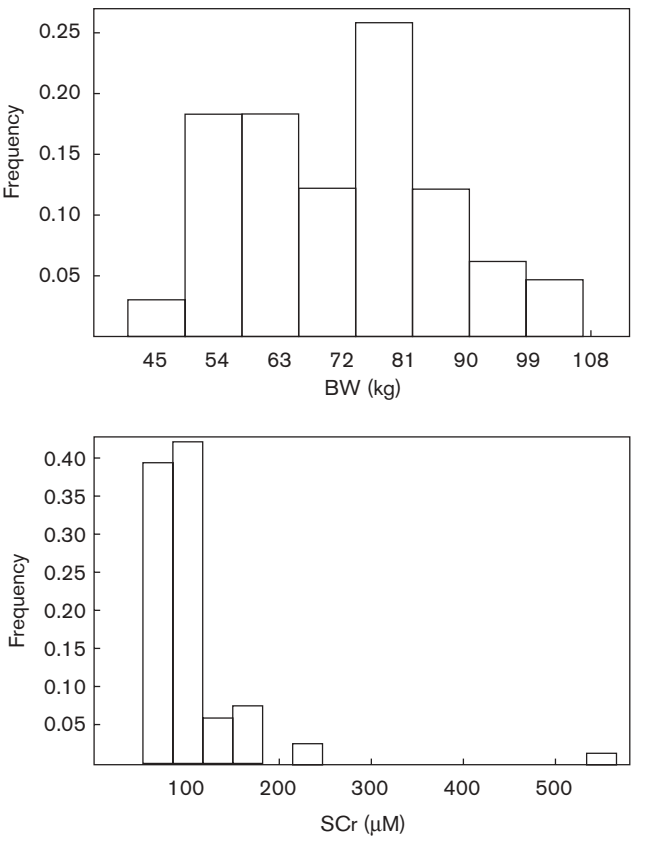
where TV(CL) is the typical value of clearance for a patient with the median covariate value and θBW is the estimated influential factor for body weight (BW). Such covariates included age, BW, BSA, serum creatinine (SCr), CGI and serum proteins. Full and reduced models (one parameter less) were compared by the χ^2 test of the difference between their respective objective function values. A change of at least 6.635 ($p < 0.01$, 1 d.o.f.) was required for the addition of a single parameter in the model. The effect of a covariate was considered to have improved the fit if there was a significant decrease in the objective function value of at least 6.635 compared to the basic pharmacokinetic model (with no covariate). An intermediate multivariate model was then obtained including all significant covariates. In order to keep only those covariates with the largest contribution to predict oxaliplatin pharmacokinetics in a final multivariate model, a change of 10.827 ($p < 0.001$, 1 d.o.f.) of the objective function was required for the retention of a single parameter during backward stepwise multiple regression analysis. At this step, reduction in the interindividual variability estimate was also considered.

Results

Demographic data

Fifty-six patients (male/female: 29/27) were available for pharmacokinetic evaluation. Fifteen patients had evidence of moderate renal impairment, as defined by a CGI < 60 ml/min. The patient's characteristics are summarized in Table 1. Figure 2 depicts the frequency of distribution of BW and SCr in the 56 patients.

Fig. 2



Frequency of distribution of BW and SCr in the patients studied.

Population pharmacokinetics

Table 1 summarizes the main characteristics of the patients studied. Fifty-six patients and 66 courses were available for pharmacokinetic evaluation. Secondary transient increases in ultrafilterable oxaliplatin concentration, including shoulder aspects, were visualized in 20 of 33 and 10 of 33 courses receiving 2- or 4-h infusions. Concentration–time courses from three patients with secondary peaks are depicted in Figure 3.

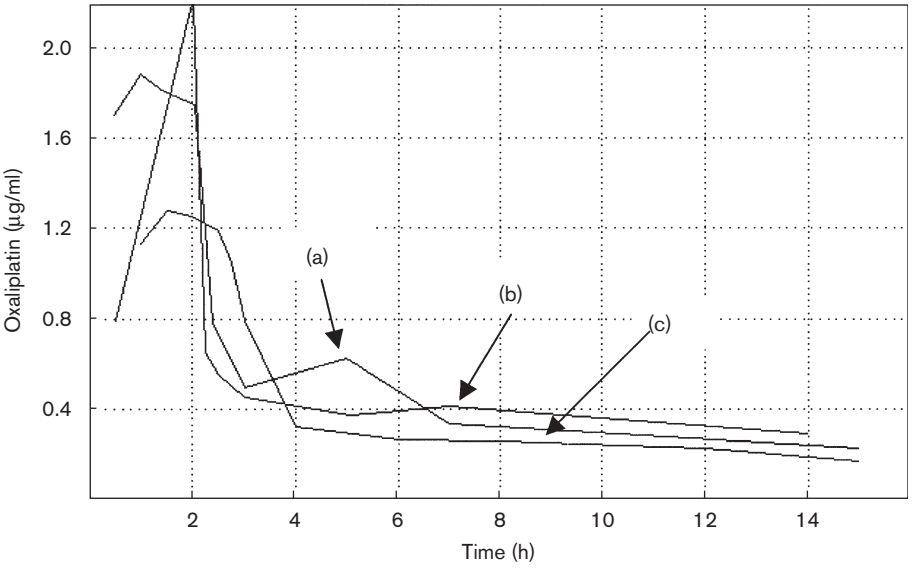
Table 1 Characteristics of the 56 patients (male/female: 29/27) studied

Characteristics	Mean	Median	Range
Age (year)	59	59	41–79
BW (kg)	71.4	71.0	41–107
BSA (m^2)	1.74	1.76	1.00–2.24
SCr (μmol/l)	104	87	53–567
CGI (ml/min)	72	66	12–157
Serum proteins (g/l)	71	72	55–85
No. of samples	537		
No. of samples per patient	8	6	4–19
Dose (mg)	169	170	72–260
Duration of infusion (h)	3.18	3.75	1.5–4.25
Ultrafilterable oxaliplatin concentrations (mg/l)	0.84	0.70	0.01–4.27

The two-compartment model with enterohepatic recirculation (EHR) adequately described the data. Compared to a simple two-compartment model, the inclusion of the EHR component reduced the objective function from –1083 to –1174 U. There was no additional benefit to use a three-compartmental model with EHR. Two representative patient curve-fittings are depicted in Figure 4. The additive component of residual variability was not significant. Thus interpatient and residual variabilities were both described by proportional error models. At this step, the inter-individual variability on k_{1B} was found not significant and exclusion of this parameter had no effect on the objective function value.

In the preliminary screening phase, the covariates that individually reduced the objective function by more than 7 U were BW, BSA, CGI and SCr. Despite an apparent difference in occurrence of secondary peak resulting from 2- or 4-h infusions, the infusion time did not significantly influence any of the EHR parameters. BW, CGI and BSA had a positive influence on CL, whereas SCr had a negative or positive influence on CL or Q. BW and BSA had a positive influence on V_1 and Q. The substitution of

Fig. 3



Observed oxaliplatin plasma concentration–time courses in three patients: (a) early secondary peak, (b) later secondary peak, and (c) a shoulder shape between times 6 and 14 h (the intra-assay error was 9%; at the lower concentration range, 0.1– 0.3µg/ml, it was 19%). Oxaliplatin actually stands for all platinum derivatives in plasma.

Table 2 Summary of effects from model verification

Model structure	Deletion of part of the model	Increase in objective function
Two compartment with EHR	EHR	91
V_1	BW effect	35
CL	BW effect	22
	SCr effect	30
	gender effect	16
Q	BW effect	26

one covariate with another was continuously explored, for strongly correlated covariates, e.g. BW and BSA. These covariates were then combined, BW or BSA, SCr, CGI and gender in a full covariate submodel. At this step, CGI could be excluded from the model. The final covariate submodeling was then:

$$\mathrm{CL} = 14.1 * \{\mathrm{BW}/71\}^{1.10} * \{\mathrm{SCr}/87\}^{-0.57} * \{0.60(\text{if female})\}$$

$$V_1 = 24.9 * \{\mathrm{BW}/71\}^{1.29}$$

$$Q = 34.8 * \{\mathrm{BW}/71\}^{1.01}$$

Substitution of BW by BSA resulted in a slight increase in objective function, −1266 versus −1282. All exclusions of individual parts of this model led to an increase of more than 11 U of the objective function value. Table 2 summarizes the effects of model verification process on the objective function value. Thereafter, the inter-individual variability of CL was decreased from 104% (basic modeling without covariates) to 62%.

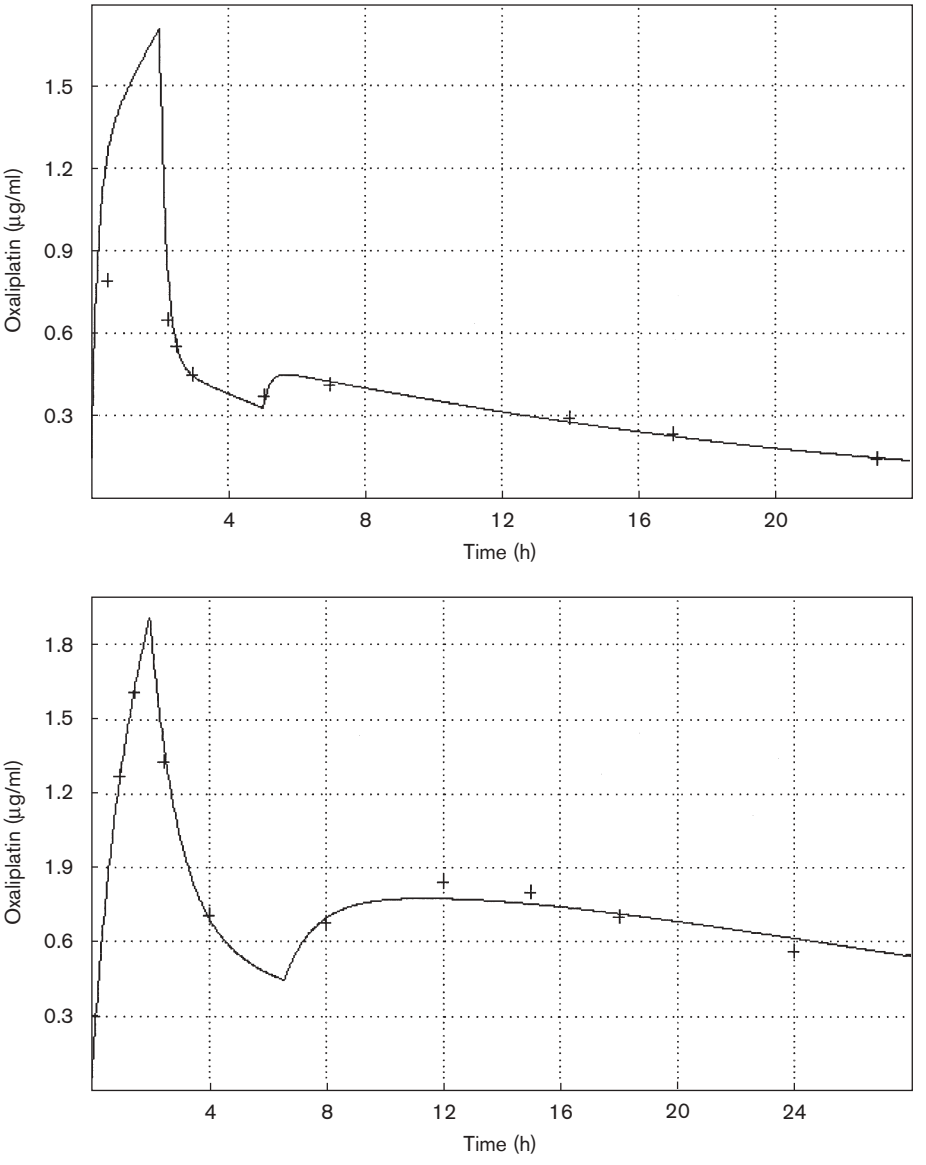
Table 3 Population pharmacokinetic parameters of ultrafilterable oxaliplatin and bootstrap validation

Parameter	Final model: original dataset		Bootstrap[a]	
	Mean	SE	Mean	SE
Structural model				
V_1 (L)	24.9	2.2	24.8	3.3
V_1, θ_{BW}	+1.29	0.30	+1.20	0.27
CL, male patients (l/h)	14.1	1.15	16.0	1.8
CL, θ_{BW}	+1.10	0.36	+1.31	0.44
CL, θ_{SCr}	−0.57	0.15	−0.69	0.16
CL, female proportionality factor	0.60	0.25	0.55	0.27
Q (l/h)	34.8	2.6	35.1	2.9
Q, θ_{BW}	+1.01	0.24	+0.85	0.39
V_2 (L)	136	13	139	13
k_{1B} (h^{-1})	1.78	0.37	1.71	0.54
T_{LAG} (h)	2.00	NE	2.10	0.24
K_a (h^{-1})	0.23	0.04	0.25	0.04
Statistical model				
residual variability, σ (%)	11.3	2.1	11.7	2.4
ω(V_1) (%)	65	33	71	50
ω(CL) (%)	62	27	64	30
ω(Q) (%)	56	23	53	18
ω(V_2) (%)	66	30	65	17
ω(T_{LAG}) (%)	282	165	300	177
ω(K_a) (%)	391	286	440	302

[a]Mean of 200 bootstrap analyses.
NE, not estimated; σ, SEM of residual variability; ω, SEM of interindividual variability.

Table 3 summarizes the final population pharmacokinetic parameter estimates and their precision. The improvement of the fit from the basic model (without covariate) to the final model is depicted in Figure 5. The precision of pharmacokinetic estimates was generally good, except

Fig. 4



Curve-fittings of representative patients using the two-compartmental open model with recirculation. Oxaliplatin actually stands for all platinum derivatives in plasma.

for the effect of gender (41% c.v.). There was a very high degree of interindividual variability for the EHR parameters, T_{LAG} and K_a.

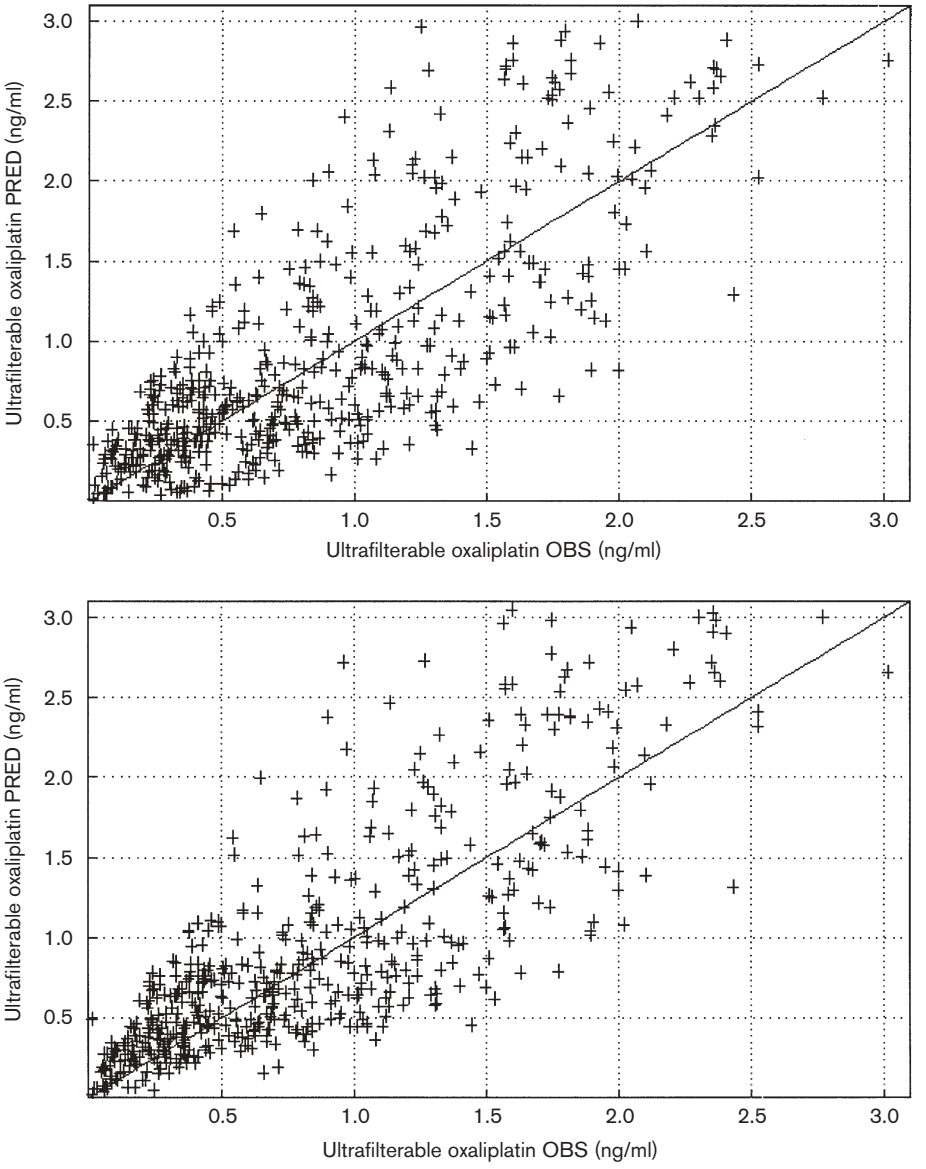
Bootstrap validation

The final model obtained with the original dataset was subjected to a bootstrap analysis. As shown in Table 3, the mean parameter estimates obtained from the bootstrap process, 200 runs, were statistically identical to the estimates previously obtained with the original dataset. There was a good concordance between both the model parameter estimates and their standard errors (SEs).

Discussion

Oxaliplatin plasma pharmacokinetics was best described by a two-compartment open model with drug recycling and first-order elimination. Previous studies using classical approaches used two- or three-compartment open models to describe ultrafilterable oxaliplatin pharmacokinetics [for a review, see ref 2]. Some transient secondary increases in oxaliplatin concentrations could also be observed in earlier reports: (i) patterns of ultrafilterable oxaliplatin time courses with clear secondary peaks [3], (ii) shoulder aspects in oxaliplatin concentration in erythrocytes [10] and (iii) a slight

Fig. 5



Predicted (PRED) versus observed (OBS) plasma ultrafilterable oxaliplatin concentrations from the basic, covariate-free, model (top) and the final pharmacokinetic model including the effects of BW, SCr and gender. Fifty-six patients, 537 concentration time points.

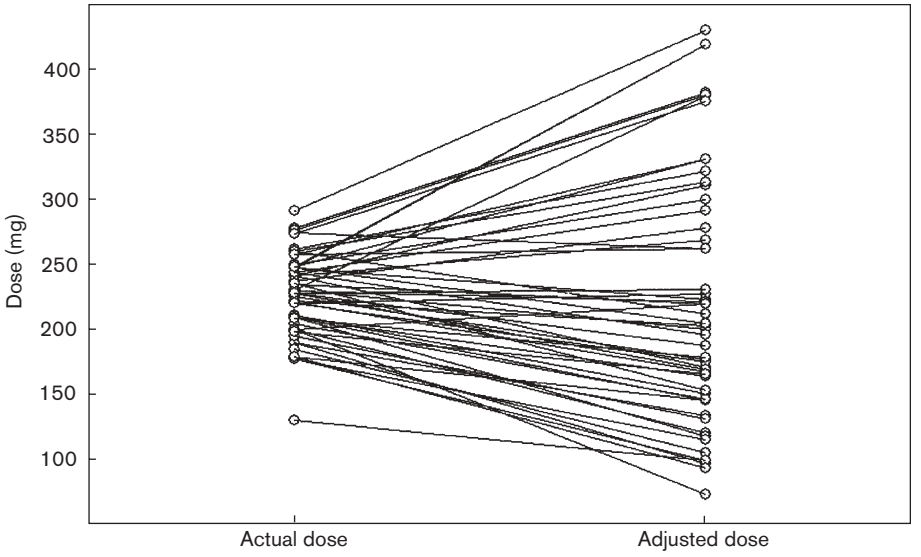
shoulder aspect in ultrafilterable oxaliplatin could be seen after a 4-h infusion around 6 h on mean concentrations versus time after 4-h infusion [11]. In most other reports, concentration–time curves reports are depicted as mean concentrations versus time, which minimizes individual deviations of patients from a theoretical model. Finally, secondary peaks were also reported during cisplatin infusions; they were attributed to a secondary influx of platinum in plasma by EHR [12]. They were mainly observed for total platinum, but the recycling was also thought to involve free platinum in order to explain longer observed half-lives and a deviation from first-order elimination.

Drug recirculation can affect terminal half-life and drug systemic exposure (AUC). Terminal half-lives of ultrafilterable oxaliplatin have been estimated from to 16 to 28 h (β phase), with a long terminal γ phase, more than 10 days [2,11]. The long half-life, γ phase is thought to represent slow release of various complexed oxaliplatin forms, so pharmacologically inactive forms. Of course, when the drug recycling is not taken into account, the

Table 4 Final population pharmacokinetic model: covariate variations that can induce a ±20% variation in systemic exposure (AUC)

Covariate	Variation in ultrafilterable oxaliplatin systemic exposure (AUC)						
	−30%	−20%	−10%	Median	+10%	+20%	+30%
BW (kg)	>98	>87	>78	71	<65	<60	<56
SCr (μM)	<46	<60	<72	87	>103	>120	>139

Fig. 6



Model-predicted oxaliplatin doses (right side) versus doses actually administered on a BSA basis to reach a target AUC of 20.35 μg/l h (left side).

secondary increases in concentration drive the curve-fitting procedure to estimate higher values of terminal half-lives than they actually are. From the present results and modeling, the terminal half-lives for male and female patients were 10.5 and 14.4 h, respectively.

Reported values for ultrafilterable oxaliplatin CL vary from 9.3 to 25.7 l/h as compiled in [2]. Our typical mean estimates, 14.1 and 8.5 l/h for male and female patients, respectively, are reasonably comparable to these previous estimates.

Several covariates with potential effect on oxaliplatin pharmacokinetics were identified, BW, BSA, SCr and gender. The influence of BW on V_1 and Q is straightforward, i.e. it can be inferred that body size parameters are related to pharmacokinetic parameters of distribution, and both V_1 and Q were influenced by BW. The covariate submodel structure for CL was the most important issue, because of the possible consequences in dosage regimen design. The covariates effects on CL were identified, both by the significant induced decrease in objective function and the visualization of Bayesian individual CL versus covariate plots. The predominance of the renal route for ultrafilterable oxaliplatin elimination is well accepted [2]. Renal function index is traditionally estimated by the CGI, that incorporates BW, SCR, age and gender for its determination. Although CGI had a significant influence on ultrafilterable oxaliplatin CL, it was found that the combination of BW, SCR and gender yielded the greatest improvement in the fit. Because BW and BSA are strongly correlated, substitution of BSA for BW in the CL formula was tested. However, this resulted in a slight increase in the objective function. This relationship between ultrafilterable oxaliplatin CL and covariates supports oxaliplatin dose normalization to BW instead of BSA, since this normalization is more straightforward. The SCr and gender terms in the CL equation also support dose adjustment for the renal function; oxaliplatin dosage should be decreased in females and in case of increased SCr. Finally, this relationship between oxaliplatin CL and BW, SCr and gender is similar to that found for carboplatin CL [13].

Table 4 summarizes the effects of changes in the significant covariates, BW or SCr, on ultrafilterable oxaliplatin systemic exposure (AUC). As expected, small variations in weight, approximately ± 15% the median value, could cause up to ± 20% change in AUC, whereas −30 to + 40% variations in SCr were necessary to cause ± 20% change in AUC.

If the therapeutic and toxic effects are believed to relate to AUC, then a prerequisite is that all of the patients should have the same oxaliplatin AUC. The usual oxaliplatin dosage is 130 mg/m^2, i.e. 230 mg/1.76 m^2. Given a median CL value, 11.3 l/h, an AUC value of 20.35 μg/l h is the pharmacokinetic endpoint. Given the individual characteristics of our patients, *a priori* oxaliplatin doses were then calculated. The potential impact of this population model for oxaliplatin dose adjustment is depicted in Figure 6.

In conclusion, this study including 56 patients with metastatic cancer showed that plasma clearance of ultrafilterable oxaliplatin was related to individual characteristics, BW, SCr and gender, that probably reflect the renal elimination of the drug. The accuracy and robustness of the model were assessed by a bootstrap method. The bootstrap results validated both the model structure and parameter estimates. If the AUC of ultrafilterable oxaliplatin is thought to constitute a pharmacokinetic endpoint, the conventional dose adjustment of oxaliplatin based on body surface area could be more simply based upon BW, along with corrections for SCr and gender effects.

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