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ORIGINAL ARTICLE

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Pharmacokinetics of platinum after oral or intravenous cisplatin: a phase 1 study in 32 adult patients

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Abstract *Aims*: To develop a population pharmacokinetic model for simultaneous analysis of oral/intravenous cisplatin data in order to estimate the mean population pharmacokinetic parameters, mainly the bioavailability, of cisplatin and to evaluate the influence of covariates on the pharmacokinetic variability. *Methods*: Pharmacokinetic and demographic data were collected from 32 adult patients (20 males/12 females, age range 47–76 years) receiving 30-min infusions or an oral formulation of cisplatin, 10–30 mg/m^2, for various malignancies. Both total plasma and ultrafilterable or unbound platinum concentrations were determined. *Results*: Unbound and total platinum concentrations were ascribed to a two-compartment model, with first-order absorption and elimination. The oral bioavailability (F) population estimates were, respectively, 0.39 and 0.30 with associated intersubject variabilities (ISV) of 24% and 26%. Peak concentrations following oral dosing occurred at 1.0 h and 1.6 h for unbound and total platinum, respectively. Clearance (CL) and central distribution volume (V_1) of unbound platinum were significantly related to body surface area (BSA). The CL and V_1 mean estimates were, respectively, 37 l/h and 23 l with an associated ISV of 15%. The final pharmacokinetic models were validated using 1000 bootstrap samples of the original datasets. *Conclusions*: Both unbound and total platinum data allowed a fair evaluation of oral cisplatin disposition, with close estimations for both absorption rates and oral bioavailability. These results also support the conventional dose adjustment of cisplatin based on BSA.

Keywords Cisplatin · Plasma binding · Population pharmacokinetics · Adults

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Introduction

There is a major trend in the development of oral chemotherapy. Pharmacoeconomic issues, as well as patient convenience and quality of life drive this. Moreover, oral chemotherapy should facilitate the use of complex treatment regimens, along with a more sustained exposure to the chemotherapeutic agent. Recently, attention has been focused on reducing the toxicity of cisplatin rather than on searching for new cisplatin analogues. To achieve this goal, some regimens consisting of cisplatin-based combinations have been established, i.e. "the use of low-dose cisplatin as a modulator of 5-FU" [9] or "the use of low-dose cisplatin in combination with radiotherapy as a radiosensitizer" [12], with the purpose of reducing cisplatin toxicity and increasing the response rate. However, oral therapy adds a substantial amount of intersubject pharmacokinetic variability, resulting in greater interpatient variations in drug exposure.

The population approach may be a useful tool to estimate the mean pharmacokinetic parameters in patients, and to identify the individual characteristics that can influence the pharmacokinetics and explain intersubject variability (ISV). The main objective of this study was to estimate the absolute bioavailability of the oral form of cisplatin in order to establish a dosage recommendation. Accordingly, population pharmacokinetic models were established to describe the time courses of unbound and total plasma platinum concentrations, and oral and intravenous data were simultaneously fitted, allowing the estimation of

pharmacokinetic parameters, including the bioavailability factor and rate of absorption.

Methods

Patients Adult patients were receiving intravenous and oral cisplatin according to an established open-label, randomized, dose-ranging, multicentric study. Patients were diagnosed with histologically documented, recurrent, nonoperable, cancer disease, requiring cisplatin plus 5-fluorouracil chemotherapy. Each patient provided written informed consent. The local Ethics Committee in France (CCPPRB) approved this study.

Cisplatin administration and assay Cisplatin was administered on five successive days either by the oral route (Ethypharm cisplatin XCP1057-2; 2.5, 5 and 10 mg capsules containing neutral microgranules coated with cisplatin and excipients), or by 30-min intravenous infusion (Bellon Cisplatyl). Patients were randomly assigned to one of the treatments on the first occasion (one occasion was defined as a course, five successive days, of chemotherapy). Thereafter, the other treatment was administered on the next occasion. The dose varied between 10 mg/m^2 and 30 mg/m^2. In each treatment group, food was allowed 2 h after the administration of cisplatin. Prior to cisplatin administration, the patients also received 1 mg of granisetron (oral) and 40 mg of methylprednisolone (intravenous).

Blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 12, 24 h after drug administration, and also just before administration and 1.5 h after administration on days 2–5. After immediate centrifugation at 1500 *g* for 10 min, the plasma was separated and an aliquot was ultrafiltered through an Amicon MPS I micropartition system with YMT membranes at 4°C for 20 min at 2000 *g* for recovery of the ultrafiltrate containing the unbound platinum species. All of the samples, plasma and ultrafiltrate, were immediately frozen at −20°C pending analysis. Platinum levels were measured by flameless atomic absorption spectrophotometric (AAS) analysis as previously described [8].

Population pharmacokinetic modelling of unbound and total plasma platinum Data were analysed using the nonlinear mixed effect modelling software program NONMEM (version V, level 1.1, double precision) with the G77 FORTRAN compiler [1]. The first-order conditional estimation (FOCE) with the INTERACTION option was used. Diagnostic graphics and distribution statistics were obtained using the R program [6]. Plasma platinum concentrations versus time from intravenous and oral administrations were simultaneously fitted using the NONMEM subroutine ADVAN4 TRANS4. Parameters of the model were V_1 and V_2 (central and peripheral distribution volumes), CL and Q (elimination and intercompartmental clearances), K_a and F (absorption rate constant and oral bioavailability fraction). Two separate analyses were conducted for unbound and total platinum. Several error models were investigated (i.e. proportional, exponential and additive error models) to describe ISV, interoccasion variability (IOV) and residual variability.

The influence of each patient covariate on pharmacokinetic parameters was tested according to the following equation, using CL as example:

$$\mathrm{CL} = \mathrm{TV(CL)} \times \{\mathrm{BW}/\mathrm{median(BM)}\}^{\theta_{\mathrm{BW}}}$$

where TV(CL) is the typical value of clearance for a patient with the median covariate value and θ_{BW} is the estimated influential factor for body weight (BW). Such covariates included gender, age, BW, height, body surface area (BSA), serum creatinine (SCr) and creatinine clearance (CrCL). CrCL was estimated by the method of Cockcroft and Gault [3]. Covariates were selected in the final population model if (1) their effect was biologically plausible, (2) they produced a minimum reduction of 4 in the objective function value (OFV), and (3) they produced a reduction in the variability of the pharmacokinetic parameter, assessed by the associated ISV.

For evaluation of the goodness-of-fit, the following graphs were compared: observed concentrations versus predictions (OBS–PRED), weighted residuals (WRES) versus time and weighted residuals versus PRED (WRES–PRED) as well as the corresponding graphs produced from the POSTHOC estimation step.

Bootstrap validation The accuracy and robustness of the final population model were assessed using a bootstrap method, as previously described in detail [11]. Briefly, this includes the following steps:

1. From the original data set of *n* individuals, B bootstrap sets (B = 1000) of *n* individuals were drawn with replacement (resampling)
2. For each of the B bootstrap sets, the population pharmacokinetic parameters were estimated
3. With the B estimates of each population pharmacokinetic parameter, the corresponding means and SD were estimated
4. To validate the model, the parameters estimated from the bootstrap had to be close to estimates obtained from the original population set.

The entire procedure was performed in an automated fashion using Wings for NONMEM [11]. This procedure also provided nonparametric statistics (median, 2.5th, 97.5th percentiles) of the population parameters.

Results

Patients Patient characteristics and some pharmacokinetic features are summarized in Table 1. For the 32 patients included, 51 cycles (26 i.v./25 oral courses), and 678 and 861 unbound and total plasma concentrations were available for modelling. Figure 1 depicts the

Table 1 Characteristics of the 32 patients studied (male/female, 20/12)

Characteristic	Mean	Median	Range
Age (years)	58	57	47–76
Body weight (kg)	63	65	40–90
Height (cm)	168	169	150–184
Body surface area (m^2)	1.71	1.74	1.38–2.13
Serum proteins (g/l)	69	70	58–80
Serum creatinine (μmol/l)	79	80.5	45–120
Creatinine clearance (ml/min)[a]	79	79.5	43–152
Dose (mg)	31	30	17.5–55
Dose (mg/m^2)	18.1	20	10–30
Intravenous administration			
Unbound platinum concentration (ng/ml)	329	160	20–1290
Total platinum concentration (ng/ml)	703	560	37–2790
Oral administration			
Unbound platinum concentration (ng/ml)	171	84	20–985
Total platinum concentration (ng/ml)	357	264	20–1800

[a]Creatinine clearance was calculated on the basis of the equation of Cockcroft and Gault [3].

pharmacokinetic concentration–time courses of unbound and total platinum.

Population pharmacokinetic analysis of unbound platinum Variance models of ISV and residual variability were best described using exponential and additive error models, respectively. The covariance term between random effects for CL and Q was found to be significant. ISV estimates for V_2 and K_a were not significantly different from zero. Further exclusion of these parameters had no effect on the OFV and did not alter the fit and the pharmacokinetic parameter estimates. This basic population model was rerun assuming each occasion was counted as a subject. There was no decrease in the resulting OFV, so the absence of IOV was concluded.

The most important factors influencing pharmacokinetic parameters, essentially V_1 and CL, were BSA, BW, CrCL and height. The decrease in OFV due to the BSA effect on CL was the greatest. In the intermediate

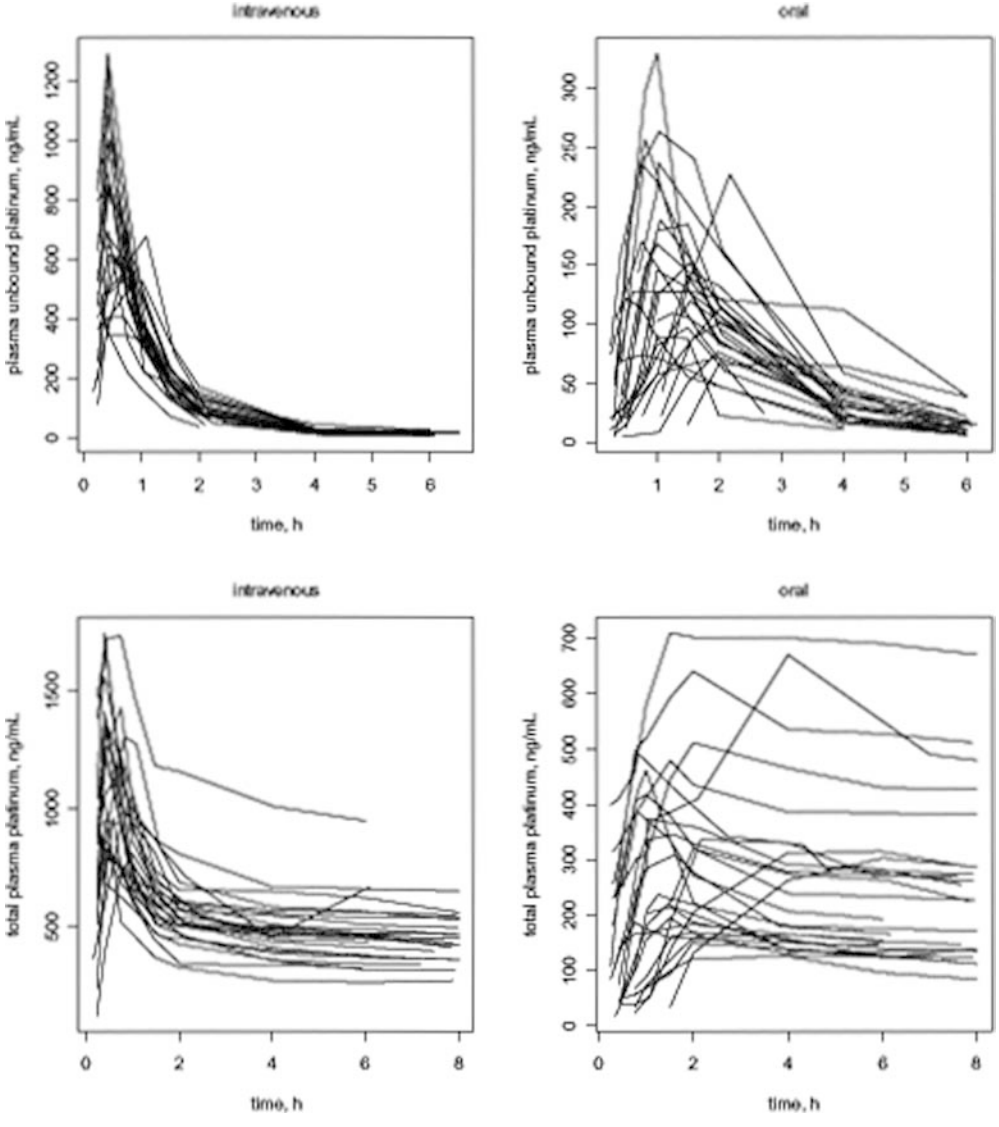

Fig. 1 Observed cisplatin unbound plasma concentration–time courses on a semilog scale

model, the effects of BSA and BSA–CrCL were tested upon V_1 and CL, respectively. Therefore, the effect of CrCL on CL became small and not significant, and the final model incorporated only BSA on V_1 and CL as follows:

$$V_1(l/h) = 22.7 \times (\mathrm{BSA}/1.74)^{+1.38}$$

$$\mathrm{CL}(l/h) = 37 \times (\mathrm{BSA}/1.74)^{+1.85}$$

Figure 2 depicts PRED–OBS and WRES–PRED scatterplots. The ISVs on CL and V_1 were reduced from 26% and 25% in the basic model (no covariate effect) to 15% and 15% in the final model. Table 2 summarizes the population estimates for the final model.

Population pharmacokinetics analysis of total platinum ISV and residual variability were best described using exponential and additive error models, respectively. The ISV estimate of K_a was not significant.

No covariate significantly influenced total platinum pharmacokinetics. Figure 3 shows PRED–OBS and WRES–PRED scatterplots. Table 3 summarizes the population pharmacokinetic parameter estimates.

Bootstrap validation The final model obtained with the original unbound or total platinum dataset was subjected to a bootstrap analysis. As shown in Tables 2 and 3, the mean parameter estimates obtained from the bootstrap process, 1000 runs were statistically identical to the estimates previously obtained with the original dataset. Moreover, the bootstrap procedure provided estimates of accuracy of the population parameters as well as nonparametric statistics of the estimates. Figure 4 shows the distribution of the unbound platinum oral bioavailability F resulting from the 1000 bootstrap estimations.

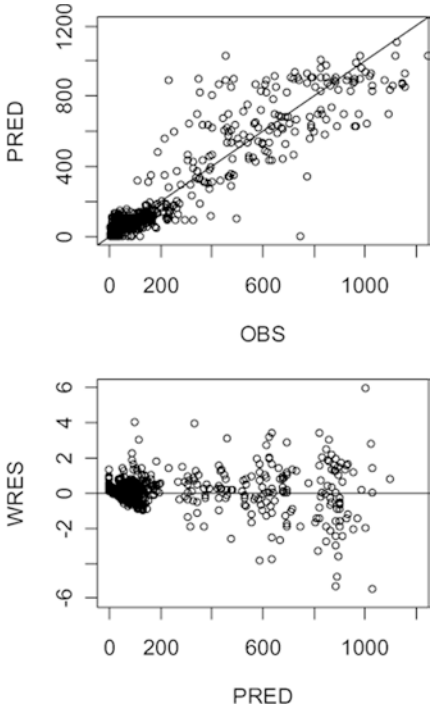

Fig. 2 Predicted (PRED) versus observed (OBS) and weighted residuals (WRES) versus predicted unbound plasma platinum concentrations from the final pharmacokinetic model including the effect of BSA on CL

Discussion

The pharmacokinetics of i.v./oral unbound platinum was satisfactorily described by a two-compartment model as already reported [2, 7, 13]. Clearance for unbound platinum ranged between 14 and 25.2 l/h (1-h infusion). In population pharmacokinetic studies, unbound platinum pharmacokinetics was ascribed to a one-compartment model, with clearance estimates of 23.5 l/h/1.74 m^2 for a 1.5-h infusion [5], 36.5 l/h/1.74 m^2 for a 2-h infusion, and 23.2 l/h/1.74 m^2 for a 4-h infusion [10]. Interestingly, in the last study, there was a clear increase in platinum CL when the infusion time was shorter. However, these population results were obtained using an HPLC technique that measured unchanged cisplatin. Our mean CL estimate, 37 l/h, is high but consistent with these previously reported values, considering the short infusion time, 0.5 h. Among the patient characteristics tested, only the BSA effect on CL and V_1 resulted in a significant improvement of the fit in this population. BSA has also been described as a proportionality factor for CL of ultrafilterable cisplatin in previous population studies [5, 10].

Table 2 Population pharmacokinetic parameters of unbound platinum and bootstrap validation (V_1, V_2 central and peripheral distribution volumes; CL, Q elimination clearance and intercompartmental clearance; K_a absorption rate constant; F oral bioavailability; BSA body surface area; σ SEM of residual variability; ω SEM of interindividual variability; ω(CL, Q) covariance value)

Parameter	Final model original dataset Mean	Bootstrap[a]		
		Mean ± SE	Median	2.5th–97.5th percentiles
Structural model				
V_1 (l)	22.7	22.8 ± 1.9	22.7	19–26
V_1, θ_{BSA}	1.38	1.49 ± 0.46	1.52	0.50–2.2
CL (l/h)	37.0	34.7 ± 8.1	37.3	17–42
CL, θ_{BSA}	1.85	1.95 ± 0.61	1.98	1–3
Q (l/h)	10.7	14 ± 10	11.5	3–28
V_2 (l)	19.5	22.5 ± 12	19	9.5–47
K_a (h^{-1})	0.65	0.65 ± 0.12	0.64	0.44–0.94
F	0.39	0.39 ± 0.04	0.385	0.30–0.47
Statistical model				
σ (ng/ml)	97	96 ± 9	96	78–110
$\omega(V_1)$ (%)	15	14 ± 5	14	3–24
ω(CL) (%)	15	16 ± 6	16.3	4–27
ω(Q) (%)	114	120 ± 44	117	43–220
ω(F) (%)	24	19 ± 6	19	6.3–32
ω(CL, Q)	0.18	0.19 ± 0.09	0.19	0.10–0.34

[a]Data from 1000 bootstrap analyses.

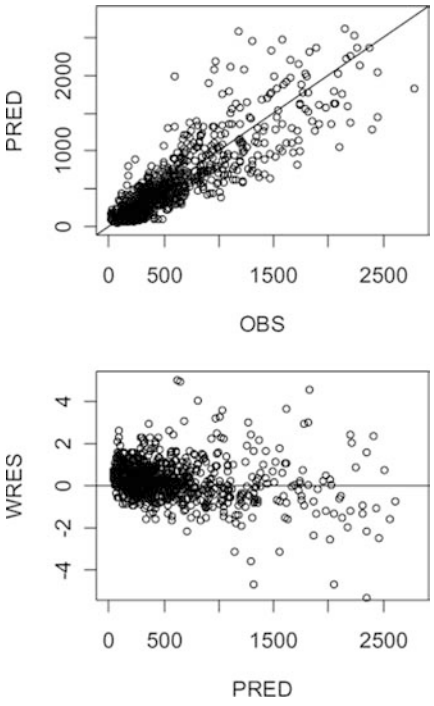

Fig. 3 Predicted (PRED) versus observed (OBS) and weighted residuals (WRES) versus predicted total plasma platinum concentrations from the final pharmacokinetic model

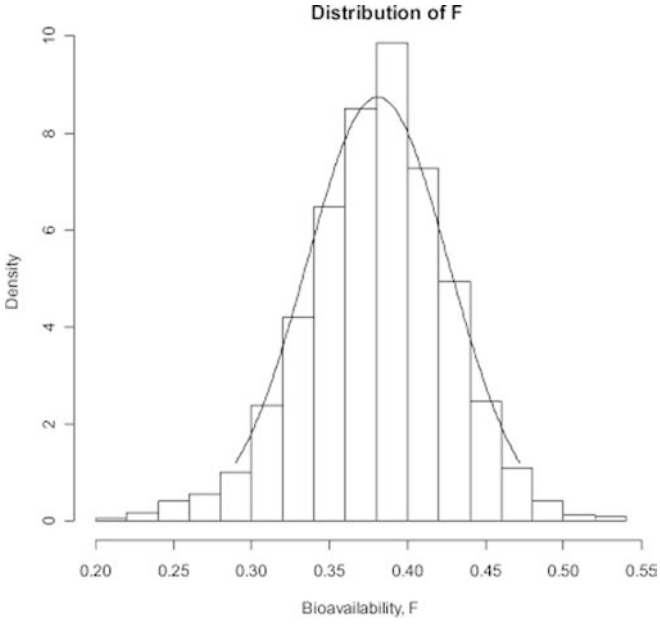

Fig. 4 Distribution of the oral bioavailability factor F for unbound platinum resulting from 1000 bootstrap analyses

Table 3 Population pharmacokinetic parameters of total platinum and bootstrap validation (V_1, V_2 central and peripheral distribution volumes; *CL*, *Q* elimination clearance and intercompartmental clearance; K_a absorption rate constant; *F* oral bioavailability; σ SEM of residual variability; ω SEM of interindividual variability)

Parameter	Final model original dataset Mean ± SE	Bootstrap[a]		
		Mean ± SE	Median	2.5th–97.5th percentiles
Structural model				
V_1 (l)	22.3	22.3 ± 1.8	22.1	19–26
CL (l/h)	0.27	0.30 ± 0.11	0.27	0.17–0.64
Q (l/h)	19	19 ± 2	19	15–23
V_2 (l)	77	78 ± 20	76	50–141
K_a (h^{-1})	0.69	0.73 ± 0.16	0.70	0.50–1.12
F	0.30	0.30 ± 0.03	0.29	0.25–0.36
Statistical model				
σ (ng/ml)	136	143 ± 62	150	53–240
$\omega(V_1)$ (%)	40	38 ± 6	38	26–51
ω(CL) (%)	62	61 ± 25	62	6–106
$\omega(Q)$ (%)	36	33 ± 8	34	17–46
$\omega(V_2)$ (%)	41	42 ± 14	40	21–86
ω(F) (%)	26	24 ± 8	25	6–36

[a]Data from 1000 bootstrap analyses.

This final covariate modelling resulted in a reduced CL ISV of 15% (vs 26% in the covariate-free model).

For total platinum pharmacokinetics, a two-compartment model has been reported [2, 7], but also a three-exponential model [4]. No individual covariate significantly influenced total platinum pharmacokinetics. Our clearance estimate for total platinum, 0.27 l/h, was much lower than platinum unbound clearance. This slow elimination rate is due to irreversibly protein-bound platinum species that constitutes most of the total plasma platinum during the post-infusion, late elimination phase.

A major objective of this study was to characterize the oral disposition of cisplatin. As a result of the simultaneous analysis of i.v./oral data, the average bioavailability and absorption rate constant were estimated even in the few patients who did not receive both routes of administration. The absorption rate constants estimated from unbound and total platinum data, 0.65 h^{-1} and 0.69 h^{-1}, were reasonably close. Time to peak concentrations were graphically estimated: 50–65 min and approximately 1.6 h for unbound and total platinum, respectively. Also, the oral bioavailability estimates were in the same order, 40% and 30%, from unbound and total platinum data, indicating that the fraction of oral dose absorbed can be reasonably approximated at 40%.

A major aim of population pharmacokinetics is to determine which measurable pathophysiological factor can cause changes in the dose-concentration relationship and to estimate the degree to which they do so, so that an appropriate dose adjustment can be made. This is particularly relevant for drugs that exhibit an appreciable degree of ISV, such as cisplatin. This study confirms previous results indicating the need to adjust cisplatin dosage on a BSA basis. Moreover, the oral disposition of a new oral formulation of cisplatin was assessed, with close estimates from both the unbound and total platinum data. Finally, it was important to determine whether these models and estimates were sufficiently accurate and robust. This was done using a bootstrap

method, which indicated that the best models were identical to those obtained with the original datasets.

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