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A limited sampling strategy for determining carboplatin AUC and monitoring drug dosage

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Abstract

There are several convincing reports showing relationships between the area under the curve of ultrafilterable concentration versus time (AUC) and pharmacodynamics of carboplatin. It is advisable, in treated patients, to check the AUC that is effectively delivered as compared with the prescribed AUC. To this end, limited sampling strategy seems to be an adequate approach since it limits the constraints of repeated blood sampling for both patients and nursing staff. A flexible limited sampling method for assessing ultrafilterable carboplatin AUC was developed. This method was based on a Bayesian estimation of carboplatin clearance using the NON linear Mixed Effect Model (NONMEN) program and a large pharmacokinetic and covariates database (103 patients). The optimal sampling design was a two-sample schedule (1 and 4 h after the end of infusion). During a prospective evaluation, it allowed an adequate estimation of carboplatin clearance with a non-significant bias (−4.5%) and a good precision (9%). In a second stage, this method was clinically applied to monitor carboplatin AUC in a group of 5 patients with metastatic germ cell tumours treated with intensified high dose carboplatin-based chemotherapy for 4 days. Dosage adjustments were performed according to daily controls of their AUC in order to obtain a total AUC of 20 mg/ml×min. By using this strategy all patients effectively received a total AUC very close to this targeted AUC, thus proving the clinical usefulness of this limited sampling method.

Keywords: Carboplatin; Limited sampling strategy; Drug monitoring

1. Introduction

There are several convincing reports showing relationships between ultrafilterable carboplatin (CBDCA) area under the curve of concentration versus time (AUC) and pharmacodynamics in treated patients. Links between CBDCA AUC and thrombocytopenia have led to the concept of targeted AUC [1] and have prompted the development of different formulas for individual dosage adaptation on the basis of physiological variables [2–4]. Retrospective studies have shown that treatment efficacy could be related to the received CBDCA AUC [5,6]. The concept of AUC dosing for CBDCA is now widely accepted.

It is advisable, in treated patients, to check the AUC that is effectively delivered as compared with the prescribed AUC. To this end, limited sampling strategy seems to be an adequate approach since it limits the constraints of repeated blood sampling for both patients and nursing staff. Limited sampling methods have been previously proposed for CBDCA. The approach described by Sorensen and colleagues [7] allows an estimation of the AUC on the basis of single sample (sampled at 2.75 h) or dual sample (sampled at 0.25 and 2.75 h) plasma drug concentrations. This model was prospectively validated for use in high-dose combination chemotherapy schedules [8]. However, this approach, based on a multiple linear regression model, is not flexible enough since it requires accurate control of both the duration of the carboplatin infusion and the time at which the samples are taken. Another method is derived from the relationship between the carboplatin ultrafilterable AUC and the total plasma concentration

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determined 24 h after treatment [9]. This method is more flexible but can be used only after the first carboplatin delivery since accumulation of platinum bound to plasma proteins occurs thereafter. Moreover, if carboplatin has to be infused daily and the dosage adjustment performed each day, determination of the 24 h total plasma concentration would delay the subsequent infusion. In a paediatric population, two Bayesian approaches have been proposed to estimate carboplatin clearance from a limited number of blood samples [10,11].

2. Patients and methods

An original limited sampling method has been developed for assessing CBDCA AUC in adult patients. This method is based on a Bayesian estimation of carboplatin clearance using the NON linear Mixed Effect Model (NONMEN) program and a large pharmacokinetic and covariates database. An optimal sampling design was determined and validated.

In a second stage, this method was clinically applied to monitor CBDCA AUC in a group of patients with metastatic germ cell tumours treated with intensified high-dose CBDCA-based chemotherapy.

2.1. Bayesian analysis using NONMEM

Bayesian estimation was performed using the NONMEN program [12] (version IV, level 1.1, POSTHOC option) and the PREDPP package (ADVAN 3, TRANS 4) [13] running on a PC (Pentium 200 pro) in order to determine the CBDCA clearance (CL) from a limited number of samples. The database consisted of 9 samples (on average) per patient in a total of 103 patients (M/F: 68/35; mean (range): age 59 (23–84) years, weight: 69 (40–112) kg, body surface area: 1.77 (1.33–2.24) m^2, serum creatinine: 117 (55–353) μM, carboplatin dose: 451 (150–975) mg). Four procedures of one sampling time were compared: 0, 0.5, 1 and 4 h after the end of a 1-h infusion. These sampling times were adopted because they were potentially available for all patients and for practical reasons (i.e. sampling time early enough to allow plasma ultrafilterable platinum analysis to be performed on the day of carboplatin administration). 15 patients were randomly selected to form the 'screening group'. In these patients, a comparison was made between their actual CLs and their CLs obtained by Bayesian estimation using the NONMEN program and the different sampling times. 13 patients were randomly selected for prospective evaluation of the model = 'validation group'. In this group, the efficacy of a two-sample procedure combining the two best single sampling times was tested. These 15 (screening group) and 13 patients (validation group) were randomly selected from the database (103 patients).

A two-compartment open pharmacokinetic model with first-order elimination was used to describe the pharmacokinetics of CBDCA. A proportional error model was used for residual and interpatient variabilities. Patient covariates were taken into account to compute the typical value of pharmacokinetic parameters: volumes of distribution with body surface area (BSA), and CL with weight, serum creatinine, age and sex according to an equation [4] established with data from patients previously studied. Typical values of central and peripheral volumes were both proportional to BSA and the typical value of clearance was:

$$\mathrm{CL\ (ml/min)} = \theta 1.\mathrm{weight} + \frac{\theta 2.\mathrm{weight}.(1-\theta 3.\mathrm{age}).(1-\theta 4.\mathrm{sex})}{\mathrm{serum\ creatinine}}$$

with weight in kg, age in years, serum creatinine in μM, and sex = 0 if male and sex = 1 if female. The actual CL was obtained individually using all data points by linear trapezoidal rule up to the last measured concentration and extrapolation to infinite time by taking the rate constant for the terminal phase (SIPHAR program, Simed, France). For a patient *j*, the relative prediction error, *pej*%, for CL was defined as follows:

$$pej\ (\%) = \frac{\mathrm{CL_{LSS}} - \mathrm{CL}}{\mathrm{CL}} \times 100$$

where $\mathrm{CL_{LSS}}$ is the Bayesian estimate of CL for patient *j*, and CL is the actual CL. Predictive performance of Bayesian estimations using the various sampling times was evaluated by computing the mean relative prediction error [$\mathrm{me\%} = \mathrm{N}^{-1}.\sum_{j=1}^{\mathrm{N}}(pej)$ where N is the number of patients] as a measure of bias and the root mean squared relative prediction error [$\mathrm{rmse\ \%} = [\mathrm{N}^{-1}.\sum_{j=1}^{\mathrm{N}}(pej))]^{1/2}$] as an assessment of precision [14].

2.2. Clinical application

The clinical part of the present study was a feasibility trial involving a group of adult male patients with metastatic germ cell tumours (see Table 3). Written informed consent was obtained and the protocol approved by the Regional Ethical Committee. Patients were in second complete remission or had a minimal residual disease and had received an intensified chemotherapy protocol at least 3 weeks after the last cycle of chemotherapy. This intensified chemotherapy protocol (CARBOPEC) consisted of etoposide 450 mg/m^2/day×4 days, cyclophosphamide 1600 mg/m^2/day×4 days and CBDCA for 4 days [15].

Table 1
Predictive performance of Bayesian estimation of ultrafilterable carboplatin clearance (CL) with different sampling times — patients in the 'screening group' ($n=15$)

Sampling time after the end of infusion	Mean CL (ml/min) (S.D.)	Bias, me % (95% CI)	Precision, rmse % (95% CI)	Correlation coefficent
Full profile: Trapezoidal rule	90 (35)	–	–	–
End of infusion	83 (29)	−10.1 (−17.9; −2.2)	16.9 (12.7; 20.3)	0.92
0.5 h	86 (28)	−0.5 (−8.9; 7.8)	14.6 (10.9; 17.5)	0.92
1 h	85 (28)	−0.4 (−4.6; 3.9)	7.4 (5.4; 9.0)	0.94
4 h	83 (29)	−4.3 (−10.1; 1.5)	11.0 (7.6; 13.6)	0.95

S.D., standard deviation; me %, mean relative prediction error; rmse %, root mean squared relative prediction error; CI, confidence interval ($\alpha=5\%$).

In a previous protocol, the dose of CBDCA was administered according to the EDTA clearance: >100 ml/min, 550 mg/m^2/day×4 days; between 60 and 100 ml/min, 400 mg/m^2/day×4 days and between 30 and 59 ml/min, 250 mg/m^2/day×4 days. Since then, wide inter-patient variability in CBDCA pharmacokinetics has been reported. For this reason, it was decided to adopt a target total AUC of 20 mg/ml×min. G-CSF was administered systematically starting at day 6 until neutrophil count >1000/mm^3. Amifostine was given to patients 2, 3 and 5 (500 mg/m^2, just before the administration of CBDCA). Patients received an autologous stem cell infusion at day 7. The initial targeted daily AUC was 5 mg/ml×min. The Chatelut formula (CL (ml/min) = 0.134.weight + [218.weight.(1−0.00457.age).(1−0.314.sex)]/ serum creatinine expressed in micromolar concentration with weight in kg, age in years, and sex = 0 if male and sex = 1 if female [4]) was used for calculating the initial dose. For patients 1 to 5, the calculated doses (mg) were as follows: 771, 757, 540, 655 and 550. But, effective starting doses were modulated according to patients' performance status. Patient 1 received more because of a good performance status whereas patients 2, 3 and 5 received less because of alterations of their performance status. It was planned that AUC on days 1 and 2 only was to be observed and doses were readjusted on days 3 and 4 so a total AUC equal to 20 mg/ml×min was obtained for all treated patients. This was done as follows: adjusted dose on day 3 and day 4 was equal to:

$$[20\ \text{mg/ml} \times \text{min} - (\text{AUC day 1} + \text{AUC day 2})] \times (\text{observed CL at day 2}) \times 0.5$$

2.3. Samples and platinum analysis

For all patients, blood samples (4 ml in heparinised tubes) were collected using an indwelling intravenous (i.v.) cannula placed in the arm not receiving chemotherapy. After immediate centrifugation at 1500*g* for 10 min, and at 4°C, the plasma was separated and ultrafiltered using the Amicon MPS1 micropartition system with YMT membranes at 4°C for 20 min at 2000*g*.

Plasma ultrafilterable carboplatin levels were measured by flameless atomic absorption spectrophotometric analysis using a 1100 B Perkin-Elmer spectrophotometer equipped with a graphite furnace [16].

3. Results

3.1. Limiting sampling strategy

Actual carboplatin clearance for patients in the 'screening' group ranged between 45 and 149 ml/min. Results of Bayesian analysis on a single sampling time are given in Table 1. The optimal time characterised by a minimal bias and the best precision was 1 h after the end of infusion. The second most effective sampling time was 4 h. Consequently, two schedules (1 h and 1 h + 4 h) were prospectively tested in the 'validation' group (13 patients): the two-sample schedule (1 h + 4 h) gave better results compared with the single-sample schedule (1 h) (Table 2). Fig. 1 shows the ratio of the estimated clearance to the actual clearance for patients of the 'validation group'; the ratio plot presentation shows that the estimated CL is generally less than the

Table 2
Prospective evaluation of the model in the 'validation group' ($n=13$)

Sampling time after the end of infusion	Prediction error: range	Bias, me % (95% CI)	Precision, rmse % (95% CI)	Correlation coefficient
1 h	−26–+20	−2.0 (−11.1; 9.1)	14.6 (8.9; 18.7)	0.83
1 h and 4 h	−21–+6	−4.5 (−9.4; 0.3)	9.0 (2.3; 12.4)	0.96

me %, mean relative prediction error; rmse %, root mean squared relative prediction error; CI, confidence interval ($\alpha=5\%$).

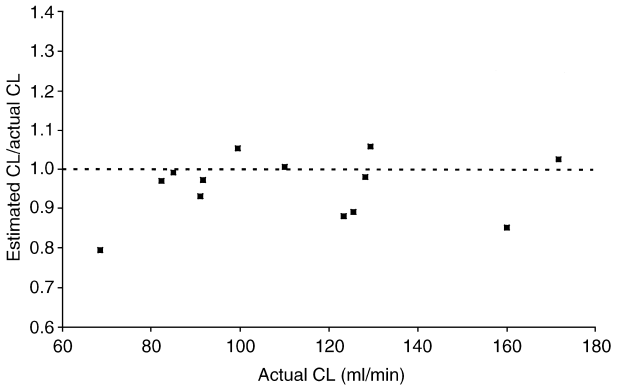

Fig. 1. Ratio plot for prospective evaluation of the limited sampling strategy in 13 patients. The estimation of carboplatin clearance values was based on concentrations at 1 h and 4 h after the end of infusion using NONMEM.

actual CL although most values are around 1. Thus, the error of prediction does not depend on the clearance value.

3.2. Clinical application

Table 3 gives the individual daily AUC values obtained by the two-sample schedule (1 h and 4 h) from the clinical application group. For all patients but one (patient 4), initial CBDCA doses were unchanged on days 1 and 2, the respective AUC were observed (initial AUCs) and in the light of these AUC values, doses were modified on days 3 and 4 so as to obtain a total AUC of 20 mg/ml×min, as scheduled. For patients 3 and 5, initial AUCs (days 1 and 2) matched very well with the targeted daily AUC (4.8 and 5.1 for patient 3, and 4.5 and 5.4 for patient 5). For this reason, CBDCA doses were not modified on days 3 and 4 and the total AUC was 19.5 for patient 3 and 20.0 for patient 5. In contrast, for patients 1 and 2, the initial AUCs exceeded the targeted AUC with values of 6.7 and 7.7 for patient 1 and 7.6 and 7.1 for patient 2. In addition, for patient 2, the dose reduction applied on day 3 led to a lower than expected AUC and for this reason the dose on day 4 was increased according to the observed clearance at day 3. For patient 4, dose modification was performed since day 2 according to the observed AUC and clearance at day 1. As assessed for patients 1, 3 and 5, the resulting total AUC was very close to the desired target value.

4. Discussion

The dual sampling time strategy (1 h and 4 h after the end of infusion) allows an adequate estimation of CBDCA CL with a non-significant bias (−4.5%) and good precision (9.0%). A single-point sampling strategy would result in slightly less precise estimates (14.6%), but it may be recommended when only one sample can be performed and/or an early estimation of the CBDCA CL is needed. This method based on Bayesian estimation using NONMEM is more flexible than the technique based on multiple linear regression models which requires accurate control of both the duration of the CBDCA infusion and the time at which the samples are obtained (i.e. samples at exactly 0.25 and 2.75 h after a 1-h infusion). The NONMEN program has been previously used for Bayesian estimation of docetaxel clearance from a limited number of samples, but the

Table 3
Clinical application: patient characteristics and carboplatin doses

Patient (age, years)	Histological type, localisation	Weight (kg)	Calculated creatinine clearance[a] (ml/min)	Doses and AUC				
		Body surface area (m^2)		Dose day 1 measured AUC[b]	Dose day 2 measured AUC[b]	Dose day 3 measured AUC[b]	Dose day 4 measured AUC[b]	Total dose Total AUC
1 (31)	Germ cell mediastinal	75 1.93	104	850 mg 6.7	850 mg 7.7	310 mg 3.8	310 mg 3.7	2320 mg 21.9
2 (32)	Embryonal testis	74 1.87	102	680 mg 7.6	680 mg 7.1	215 mg 2.2	300 mg NA	1875 mg (20)[c]
3 (35)	Embryonal testis	67 1.85	68	460 mg 4.8	460 mg 5.1	460 mg 5.0	460 mg 4.6	1840 mg 19.5
4 (40)	Choriocarcinoma testis	61 1.68	85	655 mg 6.4	460 mg NA	460 mg 4.3	460 mg NA	2030 mg (19.5)[c]
5 (41)	Seminoma testis	75 1.95	70	430 mg 4.5	430 mg 5.4	430 mg 5.3	430 mg 4.8	1720 mg 20.0

NA, blood samples not available.

[a] Creatinine clearance was calculated according to the Cockcroft and Gault formula [19].

[b] The AUC was determined according to the limited sampling strategy with the two-sample schedule (1 h and 4 h).

[c] AUC estimated by adding the measured AUC values to, for missing values (NA), AUC calculated according to the dose and clearance value of the previous day.

parameters were estimated without any patient covariate [17]. In the case of CBDCA, there is a close relationship between CL value and covariates such as the serum creatinine [4]: the coefficient of variation for interindividual variability in CL decreased from 37% (model without covariate) to 16% when covariates (serum creatinine, weight, age, and sex) were considered. As a result, in the present study, it was relevant to take into account patient covariates (i.e. serum creatinine, weight, age, and sex) amongst the a priori information. However, there is a theoretical risk of finding a patient for whom the actual CL and the typical value of CL estimated from his covariates differ greatly. In this case, the Bayesian method we use would lead to a poor adjustment of the observed concentrations. In fact, this did not occur during the prospective evaluation of the limited sampling strategy.

The clinical applicability of the limited sampling strategy was tested in a group of patients treated during a feasibility trial involving adult male patients with metastatic germ cell tumours treated by high-dose CBDCA (Table 3). The known marked interindividual pharmacokinetic variability of CBDCA necessitated individual dosing of this drug. It was initially decided to check the CBDCA AUC daily using a 4-day treatment plan including high-dose CBDCA (total AUC at 20 mg/ml×min). The AUC were merely observed on the first 2 days (AUC on days 1 and 2 was effectively obtained in 4/5 patients). It was decided to readjust the doses on days 3 and 4 in order to obtain a total AUC of 20, as scheduled by the protocol. A control at day 3 was obtained in all cases. 3 out of 5 patients had a daily control of their CBDCA AUC. In these cases, it was possible to demonstrate that the observed total AUC was very close to the planned total AUC (21.9, 19.5 and 20.0). At this stage we consider that the proposed limited sampling method for controlling CBDCA AUC is clinically applicable and allows close monitoring of a CBDCA AUC-based chemotherapy protocol. The application of the proposed model to a concrete clinical situation underlines the practical difficulty involved in systematically obtaining blood samples on a daily basis, even when a simplified sampling protocol is used. It is clear that an intensive and classical sampling schedule would not have not been feasible in this situation. However, the modifications of CBDCA clearance (dose/AUC) observed during the 4 days of administration (i.e. decrease from 127 to 82 ml/min for patient 1, and from 96 to 80 ml/min for patient 5, doses and AUC from Table 3) justify a daily monitoring of CBDCA AUC. These decreases of clearance may be a result of transitory renal insufficiency due to co-administered drugs. Comparison of the doses calculated by the 'Chatelut' equation to achieve a total AUC of 20 mg/ml×min (initial calculated dose×4) and the total dose effectively administered shows that the Bayesian approach using observed concentrations led to reduced doses in all patients. More precisely, for patients 1–5 the total dose according to the 'Chatelut' equation represented 133, 161, 117, 129, and 128% of the total administered dose, respectively. For 2 patients (2 and 4) it was already evident on day 1 that the observed AUC exceeded the AUC predicted according to the 'Chatelut' equation despite the fact that a priori a dose reduction had been performed for clinical reasons in these 2 cases. Pharmacokinetic interference due to the presence of the co-administered drugs (etoposide and cyclophosphamide) could provide a possible explanation. Amifostine was given to patients 2, 3 and 5. Korst and colleagues [18] have recently reported that, compared with a control group of patients who received CBDCA alone, patients receiving a combination of CBDCA + amifostine had a longer final half-life and a moderately increased AUC of ultrafilterable platinum. Such pharmacokinetic interference between CBDCA and amifostine could thus be suggested for patient 2 who received both drugs and exhibited a higher than expected AUC on day 1. However, patients 3 and 5 both received amifostine and exhibited an AUC very close to the prescribed value. It is thus difficult to incriminate the presence of amifostine alone as being potentially responsible for the observed higher than scheduled AUC values. The formula developed by Calvert and associates [3] to predict carboplatin clearance is based on (^{51}Cr-EDTA)-based measurement of the glomerular filtration rate (GFR), but GFR is widely substituted by the creatinine clearance calculated according to the Cockcroft–Gault formula [19]. If the Calvert formula had been applied in this way for the 5 patients, the calculated total doses (mg) would have been 2580 (patient 1), 2540 (pt 2), 1860 (pt 3), 2200 (pt 4), and 1900 (pt 5) which correspond respectively to 111, 135, 101, 108, and 110% of the administered doses. Thus, interestingly, both strategies (a priori method based on Calvert formula using the Cockcroft–Gault equation and therapeutic drug monitoring) led to similar doses for all but 1 patient (pt 2). However, the Calvert formula using the Cockcroft–Gault equation was previously shown to underpredict carboplatin clearance [20,21].

This limited sampling strategy, which has been proven clinically useful in the present study could be used for other applications. For instance, it would be interesting to apply this method during phase I studies with high-dose CBDCA escalated according to AUC values. In summary, the strategy for determining CBDCA AUC using a limited sampling strategy was validated at the pharmacokinetic level and was proven to be clinically useful by using the method to monitor a feasibility study of a CBDCA-based high-dose chemotherapy protocol. A similar strategy is currently being applied to children with refractory tumours receiving high-dose CBDCA as a single agent.

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