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A Bayesian dosing method for carboplatin given by continuous infusion for 120 h

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Abstract Carboplatin (CBDCA), an analogue of cisplatin, exhibits reduced toxicity but wide interpatient variability of its pharmacokinetic parameters. Individualization of the CBDCA dose is therefore necessary. Although various formulas have been developed for this purpose, major side effects have been reported on CBDCA administration by short-term infusion (0.5 or 1h). We therefore propose a new schedule of CBDCA administration. Instead of a dosing method based on the estimation of renal function when a classic administration schedule is used, we propose a pharmacokinetic dosing method (Bayesian method), whereby CBDCA is given by continuous infusion for 120 h. First, CBDCA was given to 21 patients to determine the population pharmacokinetic parameters of carboplatin. Then, on the basis of total platinum plasma concentration measurements and Bayesian estimation of pharmacokinetic parameters, it was possible to individualize the CBDCA dose within the first 24 h of the infusion. This new protocol for CBDCA administration was evaluated in 36 new patients (60 courses). Three theoretical end points at the end of the infusion were considered. For a given theoretical end point, 20 courses were taken into account. The theoretical end points (i.e., 1, 1.5, and 1.8 mg/l) were compared with the concentrations measured at the end of the infusion, which were 0.99 ± 0.10, 1.41 ± 0.13, and 1.72 ± 0.20 mg/l, respectively. This Bayesian dosing method can easily be used in clinical practice, and the determination of predictive performances has shown that the method is precise and unbiased. With no more toxicity or practical difficulties than those produced by other methods, and with acceptable tolerance, it was possible to reach a median dose that was 20% higher than the usual dose (484 ± 190 mg/m^2 as compared with 400 mg/m^2). In conclusion, this new schedule of CBDCA administration appears to be interesting in terms of tolerance. However, new studies are required to confirm that this new scheme leads to equal or better efficacy than the classic protocol.

Key words Carboplatin · Continuous infusion · Pharmacokinetics · Bayesian dosing method

Abbreviations *CBDCA* *cis*-Diammine(1,1-cyclobutane dicarboxylate)platinum(II) · *CDDP* *cis*-dichlorodiammineplatinum(II)

Introduction

Carboplatin (CBDCA) is an analogue of cisplatin that is currently used for various types of cancer (i.e., head and neck, urologic, and digestive cancers). It exhibits reduced toxicity as compared with cisplatin [4, 13, 24]. However, like most anticancer drugs, CBDCA has a low therapeutic index, and several authors have recommended adjustment of its dosage according to renal function [2, 3, 8, 14, 25]. Although various formulas have been proposed to individualize the CBDCA dose [3, 6], major side effects and mortality have been reported when the drug is given by short-term infusion (0.5 or 1 h) [22]. We therefore propose a new schedule of CBDCA administration. Our previous experience with cisplatin dosing [7, 11, 12] led us to use the same approach for CBDCA (i.e., administration by continuous infusion for 120 h and Bayesian estimation of pharmacokinetic parameters).

CBDCA exhibits wide interpatient variability of its pharmacokinetic parameters [9]. As an alternative to dosing methods based on renal function evaluation, we thought that it would be of interest to measure platinum

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in plasma, to estimate pharmacokinetic parameters of the patients, and to adjust the dose so as to reach a theoretical concentration at the end of the infusion. In other terms, we believed that it was possible to develop pharmacokinetic rather than nonpharmacokinetic dosing methods. Indeed, it has been demonstrated for many drugs that the latter methods are less precise than the former in the choice of the optimal dose [1]. Among pharmacokinetic methods, it is now well known that Bayesian methods exhibit excellent predictive performances and that they have become easy to use in clinical practice. However, the development of Bayesian dosing method requires a knowledge of the population pharmacokinetic parameters for the drug in question.

The aim of the present study was to develop a Bayesian dosing method for CBDCA during administration by prolonged continuous infusion (120 h). First, we determined the population pharmacokinetic parameters of total platinum using a standard two-stage method [19]. Second, this preliminary population pharmacokinetic study permitted the development of a Bayesian method that made it possible to individualize the CBDCA dose in real time for 120 h of continuous infusion. The predictive performances of this Bayesian dosing method were evaluated in 36 patients. The tolerance of this new schedule of administration was also evaluated.

Patients and methods

The study was performed in 2 phases with a total of 57 patients hospitalized in the same medical oncology ward and treated with CBDCA for various types of cancer (head and neck, colorectal, urothelial, gynecologic, lung, and metastatic tumors). During the first phase, 21 patients were included and the goal was to estimate the population pharmacokinetic parameters of CBDCA. Secondly, using the population parameters estimated in the first phase, Bayesian estimation of pharmacokinetic parameters was performed for 36 new patients (60 courses). This estimation was used to determine the optimal dose so as to reach a theoretical, previously selected optimal concentration at the end of the infusion. During this second phase the predictive performances of the Bayesian dosing method were assessed by comparison of the measured and the theoretical serum platinum concentrations.

Patients

First group – reference population

The demographic data, primitive localization of the tumor, and associated chemotherapy for the 21 patients who entered the first part of the study are shown in Table 1. All of these patients received one course of chemotherapy. This population was composed of 13 men and 8 women aged a median of 59 years (range 32–84 years). In all, 8 patients presented with head and neck cancers; 5, with genitourinary tumors; 5, with gastrointestinal cancers; 1, with lung cancer; 1, with pleural cancer; and 1, with a metastatic tumor of unknown origin.

Second group – validation population

During the second part of the study, Bayesian estimation was carried out for 36 new patients. The patients, characteristics are shown in Table 1. This population consisted of 24 men and 12 women aged a median of 55 years (range 32–72 years). Altogether, 19 patients presented with head and neck cancer; other malignancies included 5 gastrointestinal, 3 gynecologic, 2 genitourinary, 1 lung, and 6 miscellaneous types of cancers. A total of 60 courses with 3 theoretical platinum plasma concentrations at the end of the infusion (1.0, 1.5, and 1.8 mg/l) were studied (20 courses for each theoretical end point).

Some patients received several courses. For some of them the theoretical end point was always the same. Others received several courses with various maximal total platinum plasma concentrations (C_{max}). The choice of C_{max} was made by the physician on the basis of the patient's status, age, and association with radiotherapy. For head and neck cancer, when radiotherapy was associated with chemotherapy, the risk for mucosal side effects was major. In this case we used a C_{max} of 1 mg/l. For other cancers, particularly gastrointestinal cancers, the radiotherapy tolerance is generally better, and we therefore chose a C_{max} of 1.5 mg/l. When radiotherapy was not involved, the C_{max} was 1.8 mg/l.

Chemotherapy

In this study, CBDCA was given by prolonged continuous infusion at a constant rate. The same procedure has been used for cisplatin administration [11, 12] CBDCA was given by continuous infusion

Table 1 Patients' characteristics (*5FU* 5-Fluorouracil – 500 mg/day [120-h continuous infusion], *VP16* etoposide – 100 mg/day [120-h continuous infusion], *VM26* teniposide – 70 mg/m^2, *FA* folinic acid – 200 mg/m^2, *THP ADM* pirarubicin – 30 mg/m^2, *CPM* cyclophosphamide – 1000 mg/m^2, *MTC* mitomycin C – 10 mg/m^2, *RT* radiotherapy – 1.8 Gy/fraction per day [head and neck], 15 Gy/10 fractions per 5 days [gastrointestinal])

Reference population: Number of patients	Tumor	Treatment
8	Head and neck	5FU ± FA ± RT
5	Gastrointestinal	5FU ± FA ± RT
5	Genitourinary	5FU ± FA ± CPM ± THP-ADM ± VM26
1	Lung	VP16
1	Pleura	5FU ± FA
1	Unknown origin	5FU + RT

Validation population: Number of patients	Number of courses	Tumor	Treatment
19	36	Head and neck	5FU ± FA ± RT
5	10	Gastrointestinal	5FU ± FA ± MTC (± RT)
3	3	Gynecologic	5FU ± FA ± THP-ADM (± CPM)
2	3	Genitourinary	5FU ± FA ± VM26
1	1	Lung	VP16
6	7	Miscellaneous	5FU ± FA ± RT

for 120 h (5 days) using an implanted venous access port. A constant delivery rate was obtained using a volumetric pump (IVAC 591 or Abbott Shaw Life Care 4). CBDCA was diluted in 5% glucose. Perfusion hydration consisted of the infusion of 1 l of 5% glucose over 12 h. Each course of treatment was separated from the previous course by 3 weeks. Classic clinical and biologic (especially hematologic) parameters were determined for each patient.

For the reference population the dose was 500 mg (100 mg/day). For the second group of patients the mean initial dose was determined a priori by taking into account of the selected maximal concentration and the mean pharmacokinetic parameters of the reference population. These initial doses were calculated using the simulation module of the APIS program [16]. The mean initial dose was 100, 120, and 160 mg/day on day 1 for theoretical maximal concentrations at the end of the infusion of 1.0, 1.5, and 1.8 mg/l, respectively. The dose was then adjusted in real time during the infusion (at the 24th h) according to the Bayesian dosing method described below.

CBDCA was prescribed in association with other drugs (Table 1). 5-Fluorouracil and etoposide were also given by continuous infusion at a constant delivery rate for 120 h. Some patients also received radiotherapy (daily fraction of 1.5 or 1.8 Gy) concomitantly with the chemotherapy. All of the patients received anti-5-hydroxytryptamine$_3$ (anti-5HT$_3$) antiemetics to avoid nauseous side effects.

Blood sampling

Peripheral venous blood samples were taken in 5-ml heparinized glass tubes (Vacutainer, Beckton Dickinson) and centrifuged at 2000 *g* at 5 °C for 4 min. After centrifugation the plasma was immediately transferred to dry tubes and frozen at −20 °C until analysis. For the second group of patients plasma samples were immediately analyzed to allow Bayesian estimation of pharmacokinetic parameters in real time.

For each patient, blood samples were obtained immediately before the treatment (time zero), then at 1, 11.5, 12, 24, 48, 72, 96, and 120 h after the start of the infusion, and then at 3, 6 and 14 h after the end of the infusion. These collection times for blood samples were the same as those used for the dose adjustment of cisplatin [7, 12].

Analytical method

The platinum element from plasmatic CBDCA was measured by furnace atomic absorption spectrometry (FAAS; λ = 266.5 nm) using a 2380 Perkin Elmer spectrophotometer fit with an HGA300 electrothermic atomizer. This method was previously developed for cisplatin (5) and was validated for CBDCA. Plasma samples were diluted (1/10, v/v) in a nitric acid solution (5/1000, v/v) and Triton X-100 (0.5/1000, v/v). A 20-μl aliquot was injected into the apparatus. Standard solutions (10–400 ng/ml) were prepared in diluted (1/10, v/v, in water) drug-free plasma. The coefficient of variation of the method was 6% and 1.6% for platinum concentrations of 50 and 200 ng/ml, respectively. These values correspond to total platinum plasma concentrations of 0.5 and 2 mg/l, respectively. The limit of sensitivity was 20 ng/ml.

Pharmacokinetic analysis

Pharmacokinetic analysis was performed using APIS software [16] version 3.03 on an IBM PS/2 microcomputer.

Estimation of population pharmacokinetic parameters

Estimation of population pharmacokinetic parameters was performed using a standard two-stage method [20]. Individual parameters were obtained from the 21 patients of the reference population. Estimation of individual pharmacokinetic parameters was performed using a two-compartment model (with macroconstants A1, A2, a1, and a2) and a weighted least-squares estimation method. The weighting form was $1/Y^2$. The explicit formulas used in the APIS software have been extensively described elsewhere [17]. After estimation of the model macroconstants for each patient, assuming normal distribution, we computed the mean vector and the covariance matrix of the pharmacokinetic parameters.

Bayesian estimation of pharmacokinetic parameters and individualization of the CBDCA dose

Once the population pharmacokinetic parameters had been defined, Bayesian estimation was performed using only two drug plasma concentrations corresponding to the sample drawn at 1 and 12 h after the start of the infusion, respectively, for the patient concerned. This procedure was applied for the 36 patients included in the second part of the study and for a total of 60 courses of chemotherapy. For each patient, Bayesian estimation of the pharmacokinetic parameters permitted a dose adjustment at 24 h after the start of the infusion. The optimal dose was determined by simulation using the APIS software. This dose was computed according to the individual pharmacokinetic parameters to reach a concentration of 1.0, 1.5, or 1.8 mg/l at the end of the infusion. A total of 20 courses were taken into account for each theoretical end point.

Predictive performances

The predictive performances of the Bayesian dosing method were assessed as suggested by Sheiner and Beal [20]. This was performed for total platinum concentrations at the end of the infusion. The reference value was the theoretical end point, which was compared with the platinum concentration measured at the end of the infusion. Comparisons with reference values were assessed by computation of the bias and the precision [20].

The prediction error (pe) was defined as follows:

$$\mathrm{pe} = C_{theoretical} - C_{measured},$$

where $C_{theoretical}$ and $C_{measured}$ represent the reference values obtained for platinum concentration at the end of the infusion. The relative prediction error (rpe) was calculated as follows:

$$\mathrm{rpe} = \frac{C_{theoretical} - C_{measured}}{C_{measured}}.$$

Evaluation of tolerance

Mucosal and digestive side effects and the hematologic tolerance (hemoglobin, WBC, and platelet counts) were evaluated according to WHO recommendations and classified into five grades (0–IV).

Results

A representative plasma-concentration profile is presented in Fig. 1. Table 2 shows the mean pharmacokinetic parameters recorded for the 21 patients in the reference population. Total plasma clearance, half-lives, and volumes of distribution varied greatly among different patients. The estimated population pharmacokinetic parameters (mean vector and covariance matrix of the parameters) are reported in Table 3.

Individualization of the CBDCA dose was performed for a total of 60 courses in 36 patients. After Bayesian estimation of individual pharmacokinetic parameters,

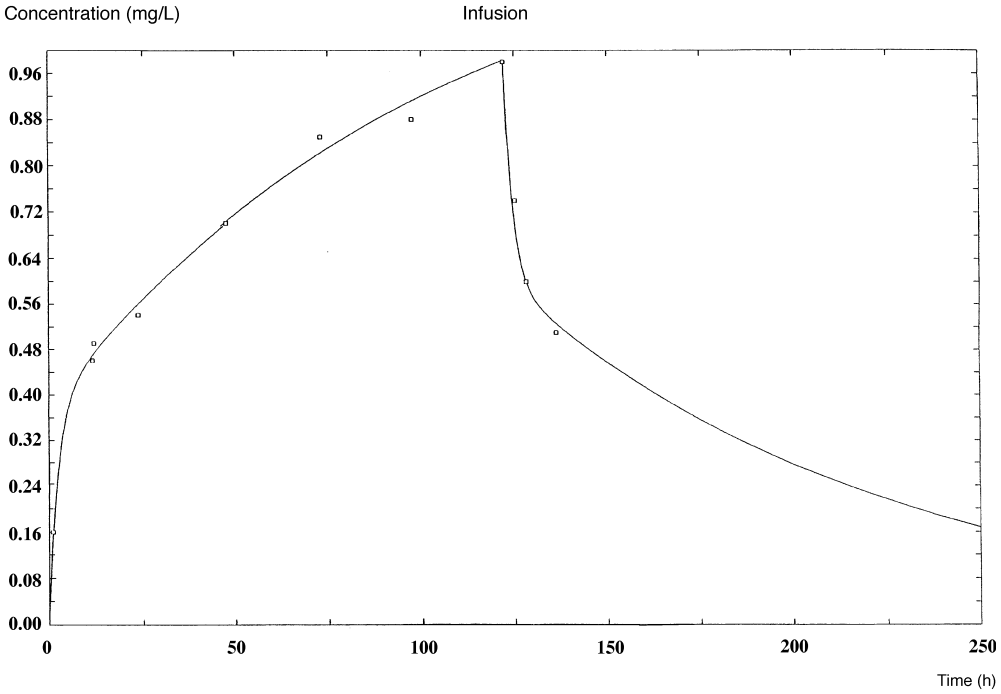

Fig. 1 Plasma-concentration profile of CBDCA

when necessary an individualization of the dose was performed for each patient entering the validation population. The details of the results observed in this second part of the study are given in Table 4 for the three theoretical end points (1.0, 1.5, and 1.8 mg/l). In all cases, more than 80% of the measured concentrations were within ± 20% of the theoretical end point. The predictive performances of the Bayesian method for carboplatin dosing are shown in Table 5. The bias was statistically significant when the theoretical C_{max} was 1.5 mg/l; however, the confidence interval showed that this bias was low. In the two other cases the bias was not statistically significant. In all cases, relative precision was satisfactory (< 20%).

From a general point of view, tolerance was excellent (Table 6). We observed grade IV ($n = 4$ cases) and grade III ($n = 2$ cases) thrombocytopenia. One case of grade III neutropenia and one case of grade III mucosal side effects were also observed. In all cases the patients received polychemotherapy.

Table 2 Pharmacokinetic parameters recorded for the reference population)[a] (C_{max} Maximal total platinum plasma concentration, AUC area under the total platinum plasma concentration versus time curve, $C1$ total plasma clearance, $t_{1/2}$ elimination half-life, V_t total volume of distribution)

C_{max} (mg/l)	1.19 ± 0.45
AUC (mg/ml) × min	15.3 ± 6.42
C1(l/h)	1.48 ± 0.65
$t_{1/2}$(h)	108 ± 49
V_t (l)	160 ± 84

[a]Results are presented as mean values ± SD

Discussion

Our results demonstrate that on the basis of total platinum plasma-concentration measurements and Bayesian estimation of pharmacokinetic parameters it is possible to individualize the CBDCA dose for 120 h of continuous infusion. This Bayesian adjustment of the CBDCA dose can easily be performed in clinical practice, and the determination of predictive performances show that the method is precise and unbiased.

Our experience in cisplatin dosing [7, 11, 12] helped us in the choice of the optimal concentration of total platinum. This protocol, which used 120 h of continuous infusion of CBDCA, was compatible with an excellent

Table 3 Pharmacokinetic parameters of the population

$$\text{Mean parameters } p = \begin{pmatrix} A1 \\ a1 \\ A2 \\ a2 \end{pmatrix} = \begin{pmatrix} 8 \times 10^{-2} \\ 46 \times 10^{-2} \\ 48 \times 10^{-4} \\ 8 \times 10^{-3} \end{pmatrix} = \begin{pmatrix} l^{-1} \\ h^{-1} \\ l^{-1} \\ h^{-1} \end{pmatrix}$$

$$\text{Covariance matrix } V = \begin{bmatrix} 3.41 \times 10^{-3} & & & \\ 1.23 \times 10^{-5} & 1.31 \times 10^{-5} & & \\ 1.44 \times 10^{-2} & 4.23 \times 10^{-5} & 7.00 \times 10^{-2} & \\ -6.44 \times 10^{-5} & 1.07 \times 10^{-5} & -2.19 \times 10^{-4} & 1.71 \times 10^{-5} \end{bmatrix}$$

Table 4 Results of CBDCA dose individualization in the validation population[a]

Number of patients	Number of courses	Theoretical C_{max} (mg/l)	C_{max} (mg/l)	Cl (l/h)	AUC (mg/ml) × min	CBDCA dose (mg)	CBDCA dose (mg/m^2)
11	20	1	0.99 ± 0.10	1.25 ± 0.40	13.1 ± 3.1 (6.65–24.6)	469 ± 130 (320–670)	282 ± 60 (211–376)
10	20	1.5	1.41 ± 0.13	1.36 ± 0.45	15.6 ± 3.7 (9.52–84.2)	600 ± 120 (370–1340)	360 ± 70 (229–724)
15	20	1.8	1.72 ± 0.20	1.38 ± 0.50	21.6 ± 7.5 (11.5–61.6)	890 ± 170 (220–1450)	484 ± 190 (169–773)

[a]Results are given as mean values ± SD (range)

Table 5 Predictive performances of the Bayesian carboplatin dosing method. Results are expressed in mg/l[a] (*RMSE* Root mean squared prediction error, *ME* mean prediction error, *S* statistically significant bias, *NS*, statistically non-significantly bias)

Theoretical C_{max} (mg/l)	Bias (ME)		Precision (RMSE)	
	Absolute	Relative (%)	Absolute	Relative (%)
1	−0.01 (−0.06 to 0.03) NS	−2.2	0.09 (0.07–0.11)	9.5
1.5	−0.06 (−0.12 to 0.01) S*	−7.6	0.13 (0.08–0.17)	17.3
1.8	−0.05 (−0.16 to 0.05) NS	−5.0	0.22 (0.08–0.31)	16.1

*$P < 0.05$
[a]Values are point estimates (and 95% confidence intervals)

clinical tolerance, although we used doses higher than those currently proposed. Using Chatelut's formula [6] for the reference population, we computed the theoretical dose to be infused if the theoretical area under the plasma concentration-time curve (AUC) were fixed at 5 (mg/ml) × min. The mean (± SD) dose computed using this formula was 572 ± 190 mg. This value was lower than the dose used in our study when the theoretical end point was 1.5 mg/l (600 ± 120 mg) or 1.8 mg/l (890 ± 170 mg).

In our study we used the measurement of total platinum. For cisplatin (CDDP), Holdener et al. [15] have shown that the AUC for ultrafilterable platinum is related to therapeutic efficacy. In a previous study with CDDP we observed that the total/ultrafilterable platinum AUC ratio was constant [7]. Although the existence of a constant ratio between total and ultrafilterable AUC remains to be proved, we decided to use total platinum measurements. Indeed, we wanted to develop a method that would be easy to apply in clinical practice. It is clear that the measurement of ultrafilterable platinum is more complex since it requires an immediate ultrafiltration step. In this context, since the plasma level of total platinum is easier to determine in clinical routine, we preferred to use this measurement instead of ultrafilterable platinum.

From a methodologic point of view we used a standard two-stage method, whereas one-stage methods (e.g., NONMEM, NPEM, NPML) have become very popular in the last 10 years [21]. It is well known that on the one hand, the use of two-stage methods is very easy, whereas on the other, these methods have some drawbacks. Indeed, a bias in the variance estimation has been demonstrated when standard two-stage methods are

Table 6 Toxicity of the treatment

C_{max} (mg/l)	Platelet count	Hemoglobin	WBC	Digestive side effects	Muscosal side effects
1	1 grade I[a] 1 grade IV[b]			2 grade I 1 grade II	1 grade I 1 grade II
1.5	1 grade II 1 grade III[b]	1 grade II[b]	2 grade I 1grade III[b]	3 grade I	1 grade II 1 grade III
1.8	2 grade I 1 grade II 1 grade III[b] 3 grade IV[b]		1 grade I 2 grade II	4 grade I 1 grade II	1 grade I[a]

[a]Cirrhotic patient
[b]Polychemotherapy

used. This problem can be very important in studies where the main objective is to describe pharmacokinetic variability in a statistical manner. However, the aim of the present study was not to describe pharmacokinetic variability but to individualize the CBDCA dose. In addition, the number of patients available for the estimation of population pharmacokinetic parameters was small ($n = 21$), whereas the number of platinum plasma concentrations obtained for a given patient was relatively high. Therefore, we chose a standard two-stage method.

Another criticism of our work is that the decline in plasma concentrations was not fully studied. Indeed, only three blood samples were drawn after the end of the infusion. However, the half-life of CBDCA is long and this study was performed in cancer patients who were hospitalized during treatment (i.e., 7 days). They returned home at 1 day after the end of the infusion, and it was difficult to ask them to stay in the hospital for scientific reasons. Nevertheless, our study demonstrated that in particular clinical situations, standard two-stage methods are very useful for the estimation of population pharmacokinetic parameters.

Concentration-time curves for total platinum in plasma after i.v. administration are usually described by three-compartment models [23]. The initial phases of distribution are generally hidden following continuous infusion. In addition, the sampling protocol (which was chosen in order to obtain pharmacokinetic parameters rapidly at the beginning of the course) did not provide a total description of the terminal phase. We therefore used a two-compartment model, and comparison with previously reported data was difficult. For the reference population the fit obtained with a two-compartment model was better than that observed with a three-compartment model. Nevertheless, our data (terminal half-life and clearance) were in good agreement with data previously obtained in studies using three-compartment models [18, 25].

From a clinical point of view, the aim of the study was not to assess the efficacy and toxicity of the treatment. However, neither nephrotoxicity nor neurotoxicity was observed. It appeared that hematologic toxic effects were the main side effects. Thrombocytopenia was related to C_{max} and was most frequent and severe (i.e., grade III and IV according to the WHO classification) in the group where the C_{max} was 1.8 mg/l. We never observed toxic death or major morbidity, although these phenomena were previously reported in a study in which Calvert's formula was used [22].

In five cases, the C_{max} was equal to or above 1.90 mg/l. In four of these five cases, thrombocytopenia was very severe (grade III and IV) and delayed the subsequent course. We therefore decided not to use the C_{max} of 1.95 mg/l, that had been considered before the study. In summary, we never observed severe toxicities.

The highest theoretical peak drug serum concentration that could be obtained without excessive toxicity was 1.8 mg/l, which corresponded to a median AUC of 360 ± 125 (mg/l) $\times$ h. In these conditions it was possible to reach a median dose that was 20% higher than the usual dose (484 ± 190 mg/m^2) as compared with the 400 mg/m^2 recommended by the pharmaceutical company (Bristol Myers Squibb).

In conclusion, continuous infusion for 120 h permits individualization of the dose of CBDCA in clinical practice as well as observation of therapeutic effects. This method is not much more difficult to apply than a short course. The delivered doses are higher by 20% than those given during short courses.

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