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SHORT COMMUNICATION

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A limited-sampling method for evaluation of the area under the curve of ultrafilterable carboplatin in children

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Abstract Carboplatin is a widely used cytotoxic agent in numerous solid tumors of children. Since there is a large degree of interpatient variability in the area under the curve of free carboplatin for a given dose of the drug, the current tendency is to adjust the carboplatin dose so as to reach a target area under the curve rather than to determine a carboplatin dose on the basis of the body surface area. A limited-sampling method was developed for estimation of the ultrafilterable carboplatin area under the curve and for adjustment of the carboplatin dose on subsequent treatments. Population parameters were obtained from 16 children (reference group). We used the maximum a posteriori (MAP) Bayesian approach on 15 children with complete carboplatin pharmacokinetic data (test group). Two blood samples were sufficient to obtain reliable prediction of the area under the curve. The best sampling times were: (a) 30 min after the end of the infusion and (b) 5 h after the end of the infusion. On the basis of these data it is possible to prescribe prospectively a target area under the curve for free carboplatin given in a fractionated daily infusion and to adapt the carboplatin dose directly to ultrafilterable carboplatin measurements.

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Introduction

Carboplatin is a widely used cytotoxic agent in numerous solid tumors of children [2], mainly because of its reduced nephro- and ototoxicity as compared with cisplatin. Its limiting toxicity is hematologic, especially thrombocytopenia. Since carboplatin may be covalently bound to plasma proteins (slower than cisplatin), the potentially active form of circulating carboplatin is free carboplatin, reflected by the ultrafilterable plasma fraction of the drug. The area under the curve (AUC) of ultrafilterable (UF) carboplatin is the main pharmacokinetic parameter correlated to toxicity [1, 5, 22] and, probably, to activity as shown in good-prognosis adult metastatic germ-cell tumors [9].

Since a large degree of interpatient variability in the AUC exists for a given dose of carboplatin [1, 14], the current tendency is to adjust the carboplatin dose so as to reach a target AUC rather than to determine a carboplatin dose on the basis of the body surface area (BSA). Since the main route of elimination of carboplatin is glomerular filtration (GFR), dose-adjustment formulae have been established in adults according to measurement of the GFR using isotopic methods [1] for minimization of the pharmacokinetic variability and reduction of the toxicity. However, the formula proposed for adults has not been validated in children, and other GFR-based formulae have been derived [11, 16]. These formulae provide a definite way to reach a target AUC for carboplatin but require either a sophisticated method for evaluation of the GFR [13, 16] or a formula taking into account the half-life of ^{51}Cr-labeled ethylenediaminetetraacetic acid (EDTA) and the total-body water content [16]. Moreover, these methods of prediction of the carboplatin clearance from a radioisotopic determination of the GFR appear to be less accurate in children than in adults [13, 16]. Conventional

measurement of the UF carboplatin AUC for dose adjustment requires unconvenient multiple blood sampling, which is especially difficult in children. Our aim was to develop a limited-sampling method for accurate estimation of the UF carboplatin AUC so as to adjust the carboplatin dose on subsequent treatments as previously described in adults [23].

Patients and methods

Patients

A total of 31 patients, including 13 girls and 18 boys aged from 9 months to 17.5 years (median 5 years), were studied (See Table 1). Patients were diagnosed with neuroblastoma (stage IV in 8 patients, localized in 3 patients), malignant mesenchymal tumor (6), high-risk retinoblastoma (5), high-risk nephroblastoma (3), esthesioneuroblastoma (2), medulloblastoma (1), peripheral primitive neuroectodermal tumor (1), and acute lymphoblastic leukemia (1). They were treated according to previously described protocols, including conventional chemotherapy in 18 cases [3, 4, 6, 8, 17] and high-dose chemotherapy with hematopoietic stem-cell rescue in 13 cases [7, 15, 19]. The total dose of carboplatin was given in one to five consecutive daily 1-h infusions and varied between 560 and 2000 mg/m^2. In most cases, carboplatin was given in association with etoposide and, for high-dose chemotherapy, with cyclophosphamide or melphalan. The protocol was approved by both institutions and informed consent was obtained from each patient, parent, or guardian as appropriate. Carboplatin (Bristol Myers Squibb, Paris La Défense, France) was diluted in 5% dextrose in sterile water and infused at a constant rate during a 1-h infusion.

Pharmacokinetics protocol

Sampling

At the beginning of this study, blood samples were taken at the following times: before the infusion, at the end of the infusion, and at 0.5, 1, 3 and 5 h after the end of the infusion. For children receiving high-dose chemotherapy with hematopoietic stem-cell rescue, the number of blood samples taken was close to 30 when the pharmacokinetics study was performed for each of the 5 days

Ultrafiltration

After immediate centrifugation at 1500 *g* for 10 min the plasma was separated and ultrafiltered through an Amicon MPS1 micropartition system with YMT membranes at 4 °C for 30 min at 2000 *g* for recovery of the ultrafiltrate containing the free platinum species. All the samples were immediately frozen at −20 °C and kept at this temperature until analysis.

Drug assay

Samples were run on a Varian Atomic Absorption Spectrophotometer AA 300 according to the previously described method [10]. Reference plasma samples spiked with increasing carboplatin concentrations were prepared every day in 5% glucose buffer, and linear regression was performed to determine patients' UF carboplatin concentration. The correlation coefficient was always higher than 0.998.

Pharmacokinetic parameter determination

The individual pharmacokinetic parameters were estimated from the UF carboplatin concentration by fitting of the data to an open two-compartment model using a weighted least-squares criterion. Log-normal distribution and a 10% coefficient of variation were assumed for the data. The pharmacokinetic parameters were then estimated with the MicroPharm program [24]. The term *observed AUC* refers to the model AUC computed from the patients' concentration data.

Individual pharmacokinetic predictions in the test group

The patients were randomized into 2 groups: 16 patients (9 boys, 7 girls) constituted the reference group, and 15 patients (9 boys, 6 girls) comprised the test group (see Table 1). Mean values and standard deviations for the population kinetic parameters were obtained from the reference group and served for the pharmacokinetic parameter estimation in the test group using the MAP Bayesian approach with a two- or three-sample strategy. The Bayesian method described by Sheiner and Beal [21] was implemented in the MicroPharm program. The following sets of sampling times were tested: [end of infusion (EOI), 5 h post-EOI], [30 min after EOI, 5 h post-EOI], [EOI, 30 min post-EOI, 5 h post-EOI], and [EOI, 5 h post-EOI, 24 h post-EOI].

The coefficient of variation in UF carboplatin clearance in the reference group was 48% and decreased to 26% and 31% when clearance was normalized by BSA and by weight, respectively. Then, average clearances corrected for BSA or weight were used to calculate an expected clearance for the test group. Thus, the AUC of each patient in the test group could be predicted from (a) the clearance based on body weight, (b) the clearance based on BSA, or (c) the clearance estimated with the MAP Bayesian method.

Results

As shown in Table 1, the sex distribution, the mean age, weight, and creatininemia did not differ significantly between the references and test groups.

The mean pharmacokinetic parameters recorded for UF carboplatin in the two groups are reported in Table 2. In the test group the individual kinetic parameters (Vc, Cl, $k12$, $k21$) were estimated from the two-point sampling, including the population parameter information, according to the Bayesian method [21].

Table 3 compares the predicted and observed AUC values recorded for UF carboplatin in the test group. For the AUC calculated by the Bayesian approach the bias between observed and predicted values varies from −25% to +27%, with the mean bias being −1% and the mean precision, 14% (Fig. 1). For the AUC predicted from the patient's BSA or weight the mean bias between observed and predicted AUC values noted for UF carboplatin are greater (both 31%). Thus, the use of these morphometric parameters would lead to a less accurate AUC prediction.

Two blood samples were sufficient to obtain a good AUC prediction. The best sampling times were (a) 30 min after infusion (except in three patients who were tested at 15 min post-EOI) and (b) 5 h after the end of the carboplatin infusion (four patients tested at 4 h post-EOI). No improvement in the accuracy of the AUC prediction was achieved by the addition of a third blood sample. When the 4- to 5-h sample was replaced by a 3-h sample the bias and precision found for the mean AUC were 20.3% and 28.5% respectively. Most of the imprecision originated from patient 15. When this patient

Table 1 Characteristics of patients in the test and reference groups

Patient number	Weight kg	BSA m^2	Age months	Creatinine μM	Sex	Dose mg/m^2
Test group: validation data set						
1	14.7	0.65	60	47	M	800
2	19.5	0.75	86	29	F	800
3	8.0	0.4	11	39	M	300[a]
4	17.0	0.72	49	36	M	600
5	16.0	0.64	44	43	M	1750
6	10.8	0.5	19	19	M	1750
7	31.8	1.06	73	32	M	1750
8	63.0	1.61	108	37	M	1000
9	14.0	0.63	60	48	F	800
10	9.4	0.44	16	15	M	1250
11	20.0	0.86	72	50	F	800
12	10.5	0.5	36	44	M	800
13	25.0	0.93	128	47	F	1250
14	23.0	0.87	74	52	F	1750
15	30.0	1.00	110	47	F	1750
Mean	20.8	0.77	63.1	39.0	9M/6F	
SD	13.7	0.31	35.3	11.2		
Reference group: population data set						
1	9.4	0.43	14	48	F	800
2	13.1	0.57	37	46	M	800
3	21.0	0.86	99	50	M	1750
4	19.3	0.78	97	67	F	560
5	16.5	0.70	61	49	F	800
6	18.6	0.74	62	40	M	1250
7	11.8	0.54	53	45	F	800
8	59.5	1.70	210	70	M	1750
9	8.3	0.40	17	36	M	800
10	21.0	0.94	121	38	M	800
11	14.4	0.60	29	33	F	800
12	13.6	0.62	40	30	M	1750
13	16.6	0.75	57	59	F	800
14	11.5	0.54	47	25	F	1750
15	41.5	1.31	174	88	M	560
16	9.2	0.42	9	29	M	200[a]
Mean	19.1	0.74	70.4	47.1	9M/7F	
SD	13.3	0.34	57.2	17.0		

[a] Total dose delivered due to the patient's age

Table 2 Mean pharmacokinetic parameters recorded for UF carboplatin in the reference and test groups (±SD)

Kinetic parameter	Reference group	Test group
Clearance (ml min^{-1} m^2)	92.8 ± 24.4	85.6 ± 32.6
Central Volume (l/m^2)	8.82 ± 3.23	8.93 ± 4.71
$k12$/min	0.0064 ± 0.0085	0.0066 ± 0.0120
$k21$/min	0.0050 ± 0.0052	0.0065 ± 0.00110

Table 3 Prediction of the UF carboplatin AUC in 15 pediatric patients: bias and precision obtained from different estimators, mean clearance normalized by BSA, mean clearance normalized by weight, and Bayesian estimated clearance

Method	Mean	Median	Range
BSA:			
Bias	31	15	−46 to 143
Precision	46	37	3 to 143
Weight:			
Bias	31	21	−46 to 187
Precision	56	45	3 to 187
Bayesian estimation:			
Bias	−1	−6	−25 to 27
Precision	14	14	6 to 27

was excluded from the analysis the bias and precision values were 7.4% and 16.2%, respectively. An attempt involving only one sampling time (0.5–1 h post-infusion) provided the following bias and precision values for the mean AUC: 11.9% and 18.8%, respectively.

Discussion

The variability in the UF carboplatin AUC determined after carboplatin infusion is well known in children [14, 16] as well as in adults [1, 5]. The variability can be reduced by individualization of doses to achieve a target AUC according to measurement of the GFR. The dose is then calculated from the target AUC and GFR values, the latter being determined by the serum clearance of a radiolabeled compound, either ^{51}Cr-EDTA [14] or [^{99m}Tc]diethylenetriaminepentaacetic acid [12].

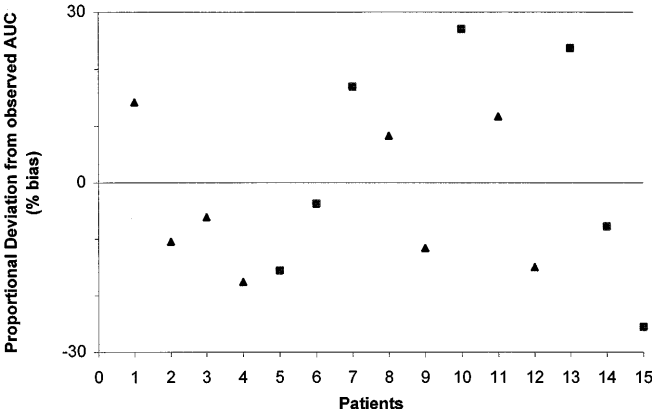

Fig. 1 Difference between the observed and predicted AUC values recorded for UF carboplatin ([*predicted*–*observed*]/*observed*) in 15 pediatric patients. Dose received ▲ below 1000 mg, ■ above 1000 mg

However, this requires sophisticated radioisotopic equipment as well as three to five blood-samples and does not avoid bias between observed and predicted AUC values recorded for UF carboplatin [14, 16].

Our limited-sampling strategy using the Bayesian approach allows the prediction of the AUC of UF carboplatin in two blood samples obtained after a 1-h carboplatin infusion. The best sampling times are around 30 min after the end of the infusion for the first sample and around 5 h postinfusion for the second one. The bias between observed and predicted AUC values recorded for UF carboplatin compares favorably with that of methods using GFR-based formulae [14, 16]. The dosage of UF carboplatin as determined by flameless atomic absorption spectrometry (despite the requirement for immediate ultrafiltration of the blood sample) is easy and reproducible in children [3, 14, 16, 20].

Moreover, our results can roughly be compared with those of Peng et al. [18] in terms of bias (median −6%, range −25% to +27%) and precision (median 14%, range 6% to 27%) for patients receiving carboplatin doses of up to 2000 mg/m^2 in 5 consecutive days. However, the true AUC was estimated by Peng et al. [18] using the trapezoidal method with extrapolation to infinity, whereas in the present study it was estimated from the model parameters.

On the basis of these data, our current aim is to prescribe prospectively a target AUC for UF carboplatin during courses in which the total dose of carboplatin is fractionated into five 1-h daily infusions. The limited sampling will be performed on day 1 or 2, dosages will be run the day thereafter, and the dose will be adapted on days 4 and 5 to achieve the expected total AUC. The aim of these clinical studies is to perform progressive AUC escalation of UF carboplatin according to hematologic and extrahematologic toxicities. Moreover, that we need only two blood samples to achieve rapid modulation of the carboplatin dose is fully compatible with the recommendations of different ethics committees with regard to the minimal number of blood sampling times leading to an immediate benefit for the patients.

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