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Clinical pharmacokinetics of carboplatin in children

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Abstract. The present study was undertaken to evaluate in children the plasma pharmacokinetics of free carboplatin given at different doses and schedules and to evaluate the inter- and intrapatient variability and the possible influence of schedule on drug exposure. A total of 35 children (age range, 1–17 years) with malignant tumors were studied. All patients had normal renal function (creatinine clearance corrected for surface body area, above 70 ml min^{-1} m^{-2}; range, 71–151 ml min^{-1} m^{-2}) and none had renal involvement by malignancy. Carboplatin was given at the following doses and schedules: 175, 400, 500, and 600 mg/m^2 given as a 1-h infusion; 1,200 mg/m^2 divided into equal doses and infused over 1 h on 2 consecutive days; and 875 and 1,200 mg/m^2 given as a 5-day continuous infusion. A total of 57 courses were studied. Carboplatin levels in plasma ultrafiltrate (UF) samples were measured both by high-performance liquid chromatography and by atomic absorption spectrophotometry. Following a 1-h infusion, carboplatin free plasma levels decayed biphasically; the disappearance half-lives, total body clearance, and apparent volume of distribution were similar for different doses. In children with normal renal function as defined by creatinemia and blood urea nitrogen (BUN) and creatinine clearance, we found at each dose studied a limited interpatient variability of the peak plasma concentration (C_{max}) and the area under the concentration-time curve (AUC) and a linear correlation between the dose and both C_{max} ($r = 0.95$) and AUC ($r = 0.97$). The mean value ± SD for the dose-normalized AUC was 13 ± 2 min m^2 l^{-1} ($n = 57$). The administration schedule does not seem to influence drug exposure, since prolonged i.v. infusion or bolus administration of 1,200 mg/m^2 achieved a similar AUC (13.78 ± 2.90 and 15.05 ± 1.44 mg ml^{-1} min, respectively). In the nine children studied during subsequent courses a limited interpatient variability was observed and no correlation ($r = 0.035$) was found between AUC and subsequent courses by a multivariate analysis of dose, AUC, and course number. The pharmacokinetic parameters were similar to those previously reported in adults; however, a weak correlation ($r = 0.52$, $P = 0.03$) between carboplatin total body clearance and creatinine clearance varying within the normal range was observed. A dosing formula appears unnecessary in children with normal renal function since a generally well-predictable free carboplatin AUC is achieved following a given dose.

Introduction

The significant antitumor activity of cisplatin is frequently accompanied by severe chronic auditory and renal toxicity [21]. In the late 1970s a number of platinum coordination complexes were synthesized in the search for a cisplatin analog with similar antitumor activity but less pronounced side effects. Among the hundreds of compounds synthesized, preclinical investigations indicated carboplatin as a possible candidate to replace cisplatin in cancer treatment. Carboplatin differs from cisplatin in that a 1,1-cyclobutane dicarboxylate group substitutes the two chlorides of cisplatin. Following the nonenzymatic hydrolysis of this ring, carboplatin is transformed into an active aquated metabolite identical to the active one of cisplatin [17, 29]. The rate of this process, which is much slower than the aquation of cisplatin, confers a lower reactivity on carboplatin and explains at least some aspects of carboplatin pharmacokinetics and pharmacodynamics, such as weak reactivity with plasma proteins and decreased nephrotoxicity [29].

In clinical studies, carboplatin has shown an antitumor spectrum similar to that of cisplatin along with less nephro- and ototoxicity but more pronounced myelotoxicity [2, 4, 5, 23]. In children the suggested dose for phase II studies was 560 mg/m^2 according to a single monthly schedule [13]

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and 175 mg/m^2 once a week for 4 weeks [1]. However, subsequent studies [14] utilizing higher doses with manageable toxicity suggested that in previously untreated adult patients at least twice the suggested doses could be safely given.

The pharmacokinetics studies performed as part of the early clinical trials suggested that a major determinant of carboplatin myelotoxicity was the plasma AUC and that the AUC was clearly dependent upon the renal excretion capability, since higher AUC values and more severe myelotoxicity were observed in patients with impaired renal excretion function [8, 16]. Studies on the clinical pharmacokinetics of carboplatin have recently been reviewed [34]; however, there are few reports on carboplatin pharmacokinetics in children [7, 22]. We report herein the results of a pharmacokinetic analysis of carboplatin in 35 children receiving carboplatin at doses varying from 175 to 1,200 mg/m^2 either as a 1-h infusion or as a prolonged continuous infusion.

Patients and methods

Patients. A total of 35 children with tumors (24 brain tumors, 2 neuroblastomas, 3 cases of acute leukemia, 1 synovial sarcoma, 1 osteosarcoma, 1 hepatocarcinoma, 1 melanoma, 1 nasopharyngeal carcinoma, and 1 Ewing's sarcoma) were included in this study. The median age was 7 years, and the age range was 10 months to 17 years. The patients included 25 boys and and 10 girls. In all, 21 patients with brain tumors were treated with preirradiation high-dose carboplatin and subsequently received alternating cycles of lomustine (CCNU) and vincristine or carboplatin and vincristine. These 21 patients were untreated when studied for the first cycle at 600 mg ×2. Ten patients with relapsed tumors had previously received nonnephrotoxic antineoplastic agents. Three patients had previously been treated with cisplatin at doses of 120, 200, and 200 mg/m^2, respectively, and one patient had received ifosfamide (total dose, 36 g/m^2).

All patients had normal hepatic and renal function and none had renal involvement by malignancy. Creatinine values were within the normal limits for the patients' age and blood urea nitrogen (BUN) levels were less than 23 mg/dl. In all patients, creatinine clearance was above 70 ml min^{-1} m^{-2} (range, 71–151 ml min^{-1} m^{-2}). Creatinine was measured by the classic method of Jaffe as modified on a Hitachi 737. Creatinine clearance was calculated according to the formula [U]×V/[P] and normalized using the formula creatinine clearance ×1.73/body surface area. In very young patients, accurate urine collection was difficult, and reliable creatinine clearance values were obtained in only 17 patients. Informed consent was obtained from the patients' families.

Drug administration. Carboplatin vials (lyophilized, 150 mg/vial with 150 mg mannitol) were reconstituted with 100 ml 0.9% NaCl and this solution was infused over 1 h. Carboplatin was given at the following doses and schedules (the numbers of courses studied are shown in parentheses): 175 (14), 400 (3), 500 (5), and 600 (15) mg/m^2 given as a 1-h infusion; 1,200 (11) mg/m^2 divided into equal doses and infused over 1 h on 2 consecutive days; and 875 (6) and 1,200 (3) mg/m^2 given as a 5-day continuous infusion. A total of 57 courses were studied, and 1–6 courses were studied in the same patient. A total of 25 patients were studied once: at 1,200 (1 patient), 875 (3 patients), 600 (11 patients), 500 (3 patients), 400 (2 patients), and 175 mg/m^2 (5 patients). In all, 5 patients were studied twice: at 175 (1 patient), 600 (2 patients), 875 (1 patient), and both 175 and 600 mg/m^2 (1 patient). The remaining 5 patients were studied three to six times at different doses. AUC intrapatient variability was studied in 9 children during up to 4 courses at the following doses: 175 (2 patients), 400 (1 patient), 600 (5 patients), and both 175 and 600 mg/m^2 (1 patient).

Sampling. Blood samples were taken at baseline, at the end of the infusion, and at 1, 2, 4, 6, 8, 12, and 24 h thereafter for the 1-h infusion schedule. In the first 10 patients, additional samples were taken during the infusion and during the 1st h after the end of the infusion. For the 5-day continuous infusion, samples were taken at baseline, at 2, 6, 12, 24, 48, 72, 96, and 120 h during the infusion, and at 2, 6, 12, and 24 h thereafter. To evaluate urinary excretion, in 15 courses at different doses (10 patients), pooled 0- to 24-h urine samples were collected and stored at 4° C. The total volume was recorded and an aliquot was stored frozen.

Carboplatin assay. A 4-ml sample of blood was immediately placed on ice and then centrifuged at 1,000 *g* for 10 min to separate the plasma. Plasma and urine were frozen at –70° C until the carboplatin analysis, which was performed within 1 week. Plasma ultrafiltrate (UF) was obtained by centrifugation at 1,500 *g* for 30 min with an Amicon MPS1 Micropartition System (cutoff, 10,000 Da). Plasma UF samples were measured both by high-performance liquid chromatography (HPLC) and by flameless atomic absorption spectrophotometry (FAAS). The HPLC assay reported by Gaver and Deeb [12] was utilized (limit of detection, 0.5 μg/ml). The CV values for intra and interassay were respectively 2% (n = 8) and 5% (n = 10) at a concentration of 25 μg/ml. Samples below the HPLC detection limit were measured by FAAS. The FAAS method of El-Yazigi et al. [9], with slight modifications in the thermal program, was used (limit of detection, 0.02 μg/ml). The coefficient of variation (CV) values were 2% (n = 7) for intraassay and 3.5% (n = 5) for interassay. In 10 patients, all samples were measured by both techniques to evaluate the percentage of intact carboplatin as compared with the total UF platinum.

Pharmacokinetic analysis. The plasma AUC was calculated from the start of the infusion by the trapezoidal rule. The plasma pharmacokinetic parameters were calculated, assuming a one- or two-compartment model according to the visual plot, from the end of the infusion. For the two compartment model the following equations were utilized:

$C = A \times e^{-\alpha \times t} + B \times e^{-\beta \times t}$

Cl = systemic clearance: dose/AUC

K_{el} = elimination constant: $\alpha \times \beta \times (A+B)/(A \times \beta + B \times \alpha)$

Vd = apparent volume of distribution: Cl/K_{el}

$t_{1/2\alpha}$ = first-phase half-life = $\ln 2/\alpha$

$t_{1/2\beta}$ = second-phase half-life = $\ln 2/\beta$

Platinum assay in tissue. The intratumoral platinum concentration was studied in a child treated with preoperative chemotherapy for a large unresectable tumor. The specimen obtained from the resected tumor was weighed (182 mg) and digested with 400 μl of a mixture of nitric and sulfuric acids (5:2, v/v) at 120° C for 2 h up to complete mineralization. Distilled water was added to the residue to a final volume of 3 ml. In all, 20 μl was analyzed by FAAS.

Results

Pharmacokinetic analyses were based on the free carboplatin plasma level since it has been shown that protein-bound platinum is devoid of antineoplastic activity [15, 33]. In 44 samples from 10 patients that were analyzed by both FAAS and HPLC, we found a FAAS-to-HPLC ratio of 0.98 ± 0.025, which suggests that carboplatin is essentially the only form of platinum-containing compound present in plasma UF. Table 1 shows the pharmacokinetic parameters of plasma UF carboplatin based on the analysis of plasma levels measured during 48 courses following i. v. administration of different doses and schedules. The mean AUC values resulting from a dose of 1,200 mg/m^2 given either as a 1-h infusion on 2 consecutive days or as a 5-day con-

tinuous infusion were very similar (15.05 and 13.78 mg ml^{-1} min, respectively).

The mean AUC values (ranges) obtained at different doses were: 2.46 (1.70–3.57) mg ml^{-1} min for the 175-mg/m^2 dose, 4.80 (3.55–5.50) mg ml^{-1} min for the 400-mg/m^2 dose, 5.30 (4.24–6.56) mg ml^{-1} min for the 500 mg/m^2 dose, and 7.42 (5.66–9.28) mg ml^{-1} min for the 600-mg/m^2 dose. The peak plasma concentration (C_{max}) was reached at the end of the 1-h infusion and increased proportionally with the dose ($r = 0.95$). The following mean C_{max} values (ranges) were obtained at different doses: 175 mg/m^2, 21.9 (16.4–28.7) μg/ml; 400 mg/m^2, 30.7 (21.0–41.0) μg/ml; 500 mg/m^2, 44.6 (35.0–54.0) μg/ml; and 600 mg/m^2, 57.6 (36.9–78.0) μg/ml. The CV values for C_{max} and AUC normalized for dose were, respectively, 22% and 18%. Values for plasma free carboplatin levels achieved with doses of 400, 500, and 600 mg/m^2 were fitted, from the end of the infusion, to a biexponential equation. For the 175-mg/m^2 dose, given the limit of sensitivity of the assay, data points were obtained only up to 8 h and the best-fitting curve was monoexponential. It appears that with the availability of data points up to 24 h, we would have observed a biexponential decay for the 175-mg/m^2 dose as well. The mean value ± SD for dose-normalized AUC was 13 ± 2 min m^2 l^{-1} ($n = 57$). The mean value ± SD for total body clearance of carboplatin was 79.9 ± 14.6 ml min^{-1} m^{-2} (range, 49–118 ml min^{-1} m^{-2}; CV, 18%). The mean value ± SD for the 24-h urinary excretion of carboplatin at different doses was 70% ± 2% of the delivered dose ($n = 15$). The alpha and beta half-lives, total body clearance, and apparent volume of distribution did not change with doses increasing from 175 to 600 mg/m^2.

Figure 1 shows the semilogarithmic plots of the mean value ± SD for plasma free carboplatin concentrations following a 1-h infusion of 175, 400, 500, and 600 mg/m^2. For the 1-h infusion schedule a linear correlation of AUC and dose was observed ($r = 0.97$, $P < 0.0001$; Fig. 2). A weak correlation of carboplatin total body clearance and creatinine clearance varying within the normal range was observed ($r = 0.53$, $P = 0.03$; Fig. 3). In the nine children studied during subsequent courses (Table 2) a limited intrapatient variability was observed in all patients but one (patient 3), and no correlation ($r = 0.035$) was found be-

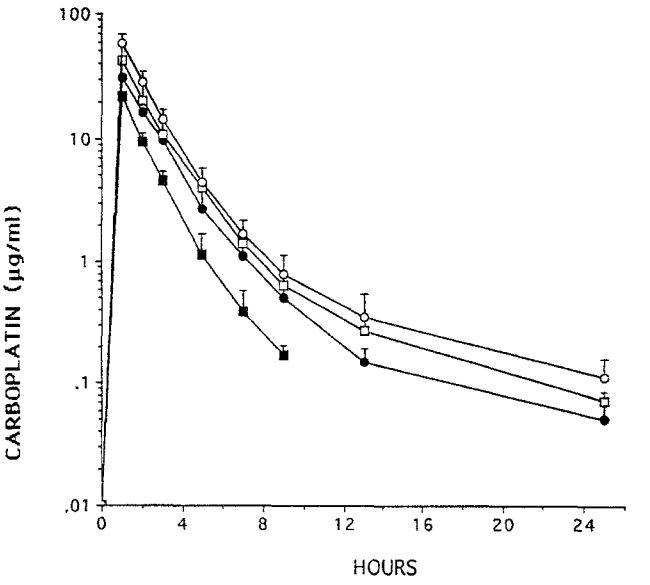

Fig. 1. Mean plasma free carboplatin levels following 1 h infusion of ■, 175 ($n = 14$); ●, 400 ($n = 3$); □, 500 ($n = 5$); and ○, 600 mg/m^2 ($n = 23$)

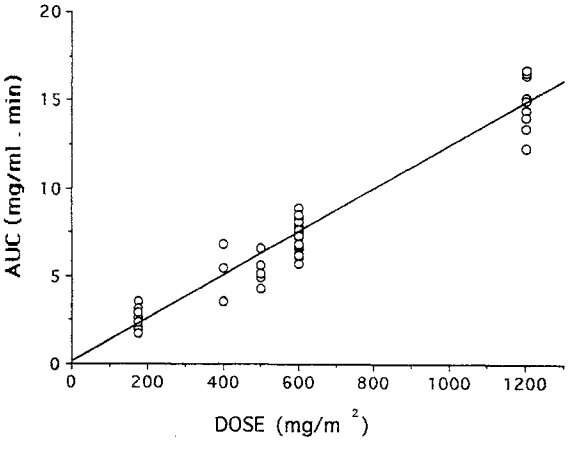

Fig. 2. Correlation of the AUC and the carboplatin dose. Mean value ± SE for the slope = 0.0123 ± 0.0004 and for the y intercept, 0.13 ± 0.27 ($r = 0.97$, $P < 0.0001$)

Table 1. Pharmacokinetic parameters of plasma free carboplatin at different doses and schedules

Dose (mg/m^2)	Schedule	Courses (n)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	C_{max} (μg/ml)	AUC (mg ml^{-1} min)	Cl/m^2 (ml/min)	Vd/m^2 (l)
175	1 h	14		1.13 (0.15)	21.9 (4.53)	2.46 (0.52)	73 (16)	7.04 (1.66)
400	1 h	3	1.05 (0.21)	6.44 (2.36)	30.69 (9.72)	4.80 (1.08)	87 (22)	8.82 (2.92)
500	1 h	5	1.14 (0.19)	6.45 (1.14)	44.6 (9.35)	5.30 (0.87)	96 (15)	10.74 (2.84)
600	1 h	26[a]	1.00 (0.18)	6.80 (1.56)	57.6 (9.9)	7.42 (1.17)	80 (12)	7.89 (1.27)
1,200	1 h × 2 days	11				15.05 (1.44)		
875	CI × 5 days	6				9.89 (3.47)		
1,200	CI × 5 days	3				13.78 (2.90)		

Data represent mean values (SD in parentheses). CI, Continuous infusion

[a] Includes data from the 1st day of treatment in 11 patients receiving 1,200 mg/m^2 over 1 h on 2 consecutive days

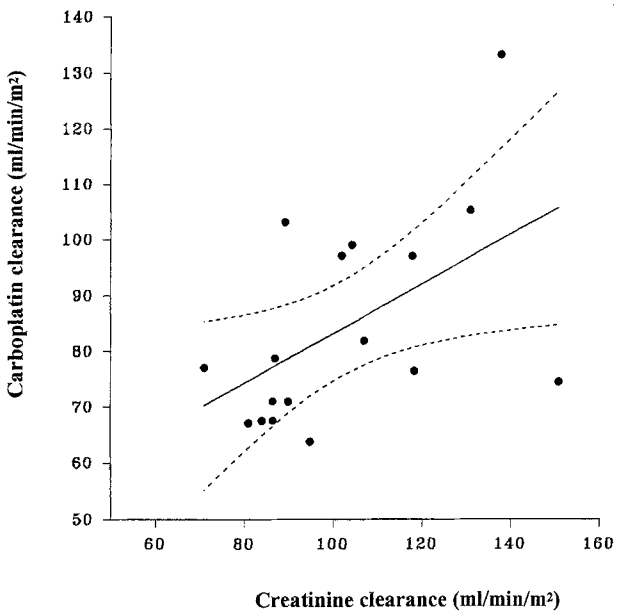

Fig. 3. Correlation of the free-carboplatin total body clearance and the creatinine clearance. The *solid line* is the linear regression line and the *broken lines* are the 95% confidence intervals. Mean values ± SE for the slope = 0.44 ± 0.19 and for the y intercept, 38.69 ± 19.42 ($r = 0.526$, $P = 0.03$)

Table 2. Free carboplatin AUC measured during repeated courses in the same patient

Patient	Dose (mg/m²)	Course	AUC (mg ml⁻¹ min)
1[a]	175	1	2.58
		2	2.68
		3	3.00
		4	2.36
2	175	1	2.41
		2	2.35
3	175	1	1.70
		2	2.94
4	400	1	6.60
		2	5.34
5	600	1	6.23
		2	6.65
6	600	1	7.14
		2	7.19
		3	8.88
7	600	1	6.57
		3	7.64
8	600	1	6.60
		2	7.44
		3	8.10
		4	6.18
9	600	1	7.85
		2	8.00
1[a]	600	1	8.45
		2	7.67

[a] This patient was studied at two different doses

tween AUC and subsequent courses by a multivariate analysis of dose, AUC, and course number.

In a patient treated with preoperative chemotherapy for a large inoperable medulloblastoma, an intratumoral platinum concentration of 0.62 μg/g wet tissue was present in the surgical specimen of tumor resected at 27 days after the administration of 1,200 mg/m² carboplatin.

Discussion

The main goals of the present study were to define the pharmacokinetics of carboplatin in children, to evaluate the possible influence of the administration schedule on drug exposure, to evaluate the inter- and intrapatient variability, and to compare our findings with previously reported adult data.

As in most recent studies on the subject, we focused on the pharmacokinetics of free carboplatin rather than total platinum since protein-bound platinum is devoid of antineoplastic activity [15, 33]. Moreover, in clinical studies, pharmacodynamic effects have been related mainly to the free carboplatin AUC [5]. In samples measured by both FAAS and HPLC methods, we confirmed that platinum in the plasma UF exists mainly as intact carboplatin, as has previously been reported [16, 26].

Carboplatin showed a biexponential decay following the 1-h infusion at all doses studied for at least 24 h and with an adequate number of samples. In most adult studies a biexponential decay of free carboplatin has been reported [10, 16, 18, 19, 24, 26, 27, 31, 35]. A shorter duration of study, mainly related to the limited assay sensitivity, has resulted in a monoexponential decay in a few reports [5, 11, 25]. Similarly, in our patients treated with 175 mg/m², data points were obtained only up to 8 h and the best-fitting curve was monoexponential. The disappearance half-lives, total body clearance, and apparent volume of distribution were independent of the the dose delivered. These pharmacokinetic parameters were very similar to the data reported in adults and in children [7, 16, 24, 26], although shorter half-lives have been reported by other authors [10, 18, 19, 22, 27, 31, 35]. These limited differences in the pharmacokinetic parameters may be the result of differences in sample numbers, sampling intervals, study duration, and initial parameter estimates.

With doses increasing from 175 to 1,200 mg/m², we observed a linear increase in both C_{max} and AUC, confirming the linear pharmacokinetics of carboplatin reported in adults by many authors [11, 16, 27, 32]. The 24-h cumulative urinary excretion expressed as a percentage of the delivered dose of carboplatin was independent of the dose and showed minimal interpatient differences, as has previously been reported [16, 18, 27].

Whereas the above-mentioned pharmacokinetic parameters are, on the whole, in good agreement with previous reports in adults, the limited interpatient variability of both C_{max} and AUC was an unexpected finding in our series of patients. This finding is in contrast with the higher variability of carboplatin clearance reported by other authors [16, 19, 26, 35] but is in agreement with the report of Shea et al. [32]. These authors found a CV of 20% for the car-

Table 3. Patients' characteristics and pharmacokinetic results reported in children treated with carboplatin

Author		Doz et al. [7]	Madden et al. [22]	Present paper
Patients studied (n)		3	18	35
Patients pretreated with cisplatin (n)		3	14	3
Duration of infusion		30 min	1 h	1 h
Dose (mg/m^2)		560	400–700	175–600
$t_{1/2}\alpha$ (min)	Mean value	67	NR	63
	Median	–	54	61
$t_{1/2}\beta$ (h)	Mean value	5.5	NR	6.45
	Median	–	3.6	6.49
Vd (l/m^2)	Mean value	8.9	NR	8.6
	Median	–	15.1	7.73
Cl_{TB} (ml min^{-1} m^{-2})	Mean value	76.5	NR	79.9
	Median	–	45.8	76.4

NR, Not reported

boplatin steady-state clearance (Cl_{ss}) in adult patients treated with high-dose carboplatin given as a 4-day continuous infusion. Recently, Madden et al. [22] studied the pharmacokinetics of carboplatin in children with relapsed solid tumors undergoing treatment with high doses of carboplatin and etoposide followed by autologous bone marrow rescue. A substantial interpatient variability of the free carboplatin AUC and a decrease in the total body clearance of carboplatin was noted. However, most patients had previously been treated with high cumulative doses of cisplatin. This may at least in part explain the differences between the findings of these authors and the results of our study (Table 3).

A dosing formula based on the glomerular filtration rate (GFR) and aiming at delivering the maximal dose of carboplatin compatible with a predefined platelet nadir was proposed by Egorin et al. [8] following initial pharmacokinetics studies in patients with normal and impaired renal function. In adults, carboplatin clearance is indeed directly correlated with GFR when measured either as creatinine clearance [8, 19] or as [^{51}Cr]-ethylenediaminetetraacetic acid (EDTA) clearance [16, 26]. It should be noted that many patients included in these studies had a moderate to severe alteration of creatinine clearance and that the correlation coefficient of carboplatin total body clearance and GFR varied from $r = 0.61$ [16] to $r = 0.82$ [8]. No good correlation of carboplatin total body clearance and creatinine clearance ($r < 0.75$) has been reported by Gaver et al. [11].

Creatinine clearance may be inadequate for the study of GFR in patients previously treated with nephrotoxic drugs, but it has been shown to be an adequate measure of renal function in previously untreated adult patients [6]. In our patients, we found a weak correlation between creatinine clearance and carboplatin clearance. Creatinine clearance may not be a reliable measure of GFR, and more precise methods should be explored such as clearance of [^{51}Cr]EDTA or [^{99m}Tc]-diethylenetriaminepentaacetic acid (DTPA). If we had measured GFR with a method more precise than creatinine clearance, a better correlation with carboplatin clearance could have become apparent. In addition, the limited number of patients in whom, for practical reasons, creatinine clearance was available may have limited the value of any AUC-creatinine clearance correlation found in our patients.

More recently, Calvert et al. [3] proposed a dosing formula simpler than that initially suggested by Egorin et al. [8] in that a predefined AUC value for UF carboplatin rather than a desired platelet reduction was chosen as the endpoint [3]. With this formula, dose is dependent mainly on GFR, the most relevant mechanism of carboplatin excretion. When applied also to patients with the above-mentioned average renal function, this formula made it possible to calculate the dose necessary to achieve the desired AUC. However, in our patients, all of whom had normal renal function, we found a weak correlation of carboplatin total body clearance and creatinine clearance, since we found a very limited interpatient variability of AUC.

These findings may have important implications, since dosing formulas have been proposed for carboplatin even in patients with a normal GFR so as to avoid under- or overexposure in patients with increased or decreased drug clearance. Given the limited interpatient variability that we observed in children with normal renal function, a dosing formula appears unnecessary since a generally well-predictable UF carboplatin AUC is achieved following a given dose.

From the linear correlation of dose and AUC shown in Fig. 2, the following formula can be derived: AUC = dose × 0.012 ($r = 0.97$, $P < 0.0001$). Calvert's formula may indeed be useful in children with impaired glomerular filtration, but this question cannot be addressed by the present study, which included only children with normal renal function. It was decided not to give carboplatin to children with altered renal function since when we started the investigation, limited data were available on possible nephro- and myelotoxicity in the presence of impaired renal function.

Dose and administration schedule are the most important variables of drug toxicity, antitumor effect, and pharmacokinetics in chemotherapy-sensitive tumors. Preclinical toxicology studies in mice have shown that continuous infusion as compared with bolus injection allows the administration of a larger quantity of drug [20]. In our patients receiving 1,200 mg/m^2, however, there was no difference in the AUC achieved, whether the same dose was given as a 1-h infusion on 2 consecutive days or as a 5-day continuous infusion. Given the relationship between AUC and myelotoxicity, these findings appear to be in agreement with the report of Leyvraz et al. [20], who compared in adults the 24-h continuous-infusion schedule with 1-h administration and found essentially the same degree of toxicity in patients treated with the same dose given according to the two different schedules. Obviously, when equal AUC values are achieved using different schedules, tumor biology becomes the most important factor as far as the antitumor activity is concerned.

Following repeated courses of carboplatin, we observed a limited intrapatient variability and a constant AUC, whereas with repeated courses of cisplatin, an increase of up to 70% in the UF AUC has been noted [28]. This result

could in some way be anticipated since carboplatin is devoid of nephrotoxicity, which is the main cause of the decreased renal clearance of cisplatin observed following repeated courses.

The intratumoral platinum level measured in a medulloblastoma surgical specimen removed 27 days after treatment with 1,200 mg/m^2 carboplatin was lower than that reported by Newell et al. [26] in an autopsy specimen of a primary lung tumor obtained 14 days after a dose of 1,600 mg/m^2. The lower platinum concentration found in our study have been due both to the longer interval between carboplatin administration and measurement (27 v 14 days) and to the influence of the blood-brain barrier on CSF carboplatin pharmacokinetics [30].

In conclusion, in children with normal renal function, free carboplatin displays a limited interpatient variability of both C_{max} and AUC and a schedule-independent drug exposure. The pharmacokinetic parameters were similar to those previously reported in adults; however, a weak correlation of carboplatin total body clearance and creatinine clearance varying within the normal range was observed. A dosing formula appears unnecessary in children with normal renal function since a generally well-predictable free carboplatin AUC is achieved following a given dose. Besides its limited chronic toxicity, the reliability of carboplatin pharmacokinetics should encourage its use as a substitute for cisplatin in the treatment of platinum-sensitive tumors.

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