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ORIGINAL ARTICLE

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Pharmacokinetically guided dosing of carboplatin in paediatric cancer patients with bilateral nephrectomy

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Abstract An approach to carboplatin dosing in children with bilateral nephrectomy using a renal function-based dosing formula with a glomerular filtration rate of zero was investigated in the current study. Carboplatin exposure was determined in a total of nine courses of chemotherapy in four patients with Wilms' tumour. Carboplatin exposures following initial dosing were less than 50% of the defined target area under the plasma concentration-time curve (AUC) in all four patients studied, with actual AUC values of between 31% and 45% of the target exposures. The use of real-time pharmacokinetic monitoring to guide dosing within a course of carboplatin treatment resulted in exposures within 15% of the target AUC in all patients. Using this information to guide dosing on additional courses of treatment in the same patient resulted in consistent exposures without the need for further monitoring or dose adjustment. These results indicate that real-time pharmacokinetic monitoring of carboplatin treatment plays a key role in ensuring that an appropriate exposure to carboplatin is achieved in children with bilateral nephrectomy. Carboplatin dosing based on patient body weight, or use of a fixed dose of carboplatin, would both be predicted to result in individual patients receiving unsatisfactory drug exposures. Further studies are warranted to further elucidate the relationship between non-renal clearance of carboplatin and patient body weight in this and other patient subpopulations where there remains concern about the optimal way to use this anticancer drug.

Keywords Carboplatin · Paediatric · Bilateral nephrectomy · Pharmacokinetics

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Introduction

The anticancer agent carboplatin is commonly used in paediatric oncology and currently plays a key role in the treatment of malignancies such as germ cell tumours, brain tumours, neuroblastoma and Wilms' tumour [2]. As the pharmacokinetics of carboplatin are largely determined by the renal function of the patient being treated, formulae have been devised to calculate the dose of carboplatin required to achieve the desired target exposure or area under the concentration-time curve (AUC) [7, 9]. These formulae commonly involve two components, one dependent on renal function and the second dependent on body surface area or weight. This secondary component reflects the non-renal clearance of carboplatin, commonly associated with irreversible protein binding of platinum species, and accounts for a relatively small percentage of the total clearance of carboplatin in patients. Use of the Newell formula to dose children based on renal function has been shown in a randomized, cross-over study to result in more consistent exposure to carboplatin than dosing based on body surface area [10]. This approach to carboplatin

dosing has now become widely accepted, with an increasing number of paediatric clinical study protocols including carboplatin dosed to a target AUC, using equations based on renal function. The rationale for this approach is supported by the observation that carboplatin AUC is correlated more closely than drug dose with both clinical toxicity and response in adults and children [3, 8].

As carboplatin is predominantly excreted by the kidneys, significant dose reduction would be expected for the treatment of anephric patients and patients with renal failure [4]. Previously published work in this area, based on a limited number of patients, has indicated that the use of renal function-based dosing formulae is feasible, and indicates the importance of the timing of haemodialysis on carboplatin pharmacokinetics [1, 5]. In patients with bilateral nephrectomy, renal function-based dosing using a glomerular filtration rate (GFR) of zero inserted into carboplatin dosing equations, equates to dosing based on body size or weight.

The dosing of carboplatin in anephric children was investigated in the current study with regard to the accuracy of renal function-based dosing formulae, and the use of pharmacokinetically guided dosing for patients receiving carboplatin treatment over several days.

Materials and methods

Patients

Four patients with bilateral nephrectomy undergoing regular haemodialysis were given chemotherapy with carboplatin in combination with etoposide for the treatment of Wilms' tumour (see Table 1). A pharmacokinetic monitoring approach to carboplatin treatment was utilized in these anephric children due to concerns regarding unpredictable exposure to a drug whose pharmacokinetics are predominantly determined by renal function. Patients were treated at the Birmingham Children's Hospital, Our Lady's Hospital for Sick Children, Dublin, Great Ormond Street Hospital, London, and St James's Hospital, Leeds, between September 2001 and September 2003.

Calculation of carboplatin dosage

The dose of carboplatin for each patient on day 1 of treatment was calculated using the renal function-based dosing formula devised by Newell et al. [9], assuming a GFR of zero, as follows:

$$\text{Dose} = \text{target AUC (mg/ml min)} \times [\text{GFR (ml/ min)} + (0.36 \times \text{BW (kg)})] \quad (1)$$

where AUC is the target area under the free-platinum plasma concentration curve and BW is the body weight of the patient. The target AUC was defined by the centre treating the individual child based on clinical status and previous chemotherapy administered to the patient. Carboplatin was administered to all patients as a 60-min infusion on each of 2 or 3 days of chemotherapy. Doses of carboplatin on subsequent days of treatment were determined following pharmacokinetic analysis so as to achieve an exposure as close as possible to the defined overall target AUC for each patient. The actual doses of carboplatin, number of days of treatment and target AUC values for each patient are shown in Table 2. All patients had samples taken for pharmacokinetic analysis, with two patients monitored on a single course of carboplatin chemotherapy, one patient on each of three courses of treatment, and one patient on each of four courses. For those patients studied on more than one course of treatment, the dose on day 1 of additional courses was usually modified from that calculated from Eq. 1, depending on the carboplatin exposure obtained on the first course of treatment. In all cases, haemodialysis was not initiated until at least 15 h after the end of carboplatin administration. For comparison, data from an additional five anephric patients have been included. Data for these patients have been published previously [1], or are from patients dosed according to Eq. 1, but with limited pharmacokinetic and clinical data.

Pharmacokinetic sampling and analysis

Blood samples (2 ml) for pharmacokinetic analysis were obtained from a central line prior to carboplatin infu-

Table 1 Characteristics of patients studied and haematological toxicity after all courses of treatment

Patient	Sex	Age (years)	Body weight (kg)	Surface area (m^2)	Carboplatin course	Nadir neutrophil count ($\times 10^9$/l)	Nadir platelet count ($\times 10^9$/l)
1	F	1.9	10.0	0.49	1	2.3	25
2	M	4.7	16.5	0.70	1	0.14	18
3	F	2.5	10.7	0.51	1	1.0	77
					2	1.6	23
					3	0.6	8
4	F	5.1	14.0	0.62	1	0.01	<20
					2	0.78	<20
					3	0.45	<20
					4	0.88	<20

Platelet transfusions were given to patients 1 and 4 following chemotherapy

Table 2 Carboplatin treatment and exposure for all courses of treatment (*ND* not determined)

Patient	Carboplatin course	Target AUC (mg/ml min)	Predicted dose[a] (mg/day)	Actual dose (mg)			AUC (mg/ml min)			
				Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Total
1	1	10	18	18	18	–	1.4	1.7	–	3.1
2	1	8	16	16	45	45	1.2	4.3	3.6	9.1
3	1	10	19	19	100	–	1.6	ND	–	ND
	2	10	19	19	42	–	3.0	6.0	–	9.0
	3	10	19	30[b]	50	–	1.9	7.3	–	9.2
4	1	10	15	15	40	40	1.5	4.9	6.1	12.5
	2	10	15	23[b]	23	23	3.1	2.9	2.9	8.9
	3	10	15	23[b]	23	23	2.6	3.1	2.9	8.6
	4	10	15	23[b]	23	23	2.3	3.2	3.3	8.8

[a]Predicted dose calculated by the Newell formula based on renal function and body weight: dose = target AUC (mg/ml min) × [GFR (ml/min) + (0.36 × BW (kg))]

[b]Day 1 dose based on carboplatin exposure on previous course of treatment

sion, 30 min after the start of infusion, at 60 min (end of infusion), and at 120 and 240 min after the start of infusion (60 and 180 min after the end of infusion). All samples were taken from a separate lumen from that used for drug administration. Plasma was separated from whole blood by centrifugation (1200 *g*, 4°C, 10 min) and 1 ml was then removed and placed in an Amicon Centrifree micropartition unit with a 30,000 Da molecular weight cut-off (Millipore, Edinburgh, UK). This plasma sample was centrifuged (1500 *g*, 4°C, 15 min) to obtain plasma ultrafiltrate for determination of free carboplatin levels. All samples were stored at −20°C prior to analysis.

Platinum pharmacokinetic analyses were carried out by flameless atomic absorption spectrophotometry (AAS) using a Perkin-Elmer Analyst 600 graphite furnace spectrometer (Perkin-Elmer, Beaconsfield, UK). Free or unbound platinum levels were determined in plasma ultrafiltrates as previously described [10]. All samples were analysed in duplicate and values are expressed as the average of these measurements. Duplicate values were within 15% of each other in all cases. Intraassay and interassay coefficients of variation for a quality assurance sample had to be $<10\%$ for an assay to be valid. The limit of detection for the AAS was 0.10 μg/ml.

The AUC of carboplatin was determined using the trapezoidal method with extrapolation to the time of initiation of dialysis, with further pharmacokinetic analysis carried out using WinNonlin (Pharsight Corporation, Mountain View, Calif.).

Results

Carboplatin doses and resulting exposures to free platinum on each day of treatment are shown for all courses of chemotherapy in Table 2. For all patients, the dose of carboplatin on day 1 of the first course of treatment, was determined using Eq. 1 above.

Both patients 1 and 2 were studied on a single course of treatment. Patient 1 received carboplatin on each of 2 days of treatment, with the dose calculated to obtain a total AUC value of 10 mg/ml min; patient 2 received 3 days of chemotherapy, with a dose designed to obtain an overall AUC of 8 mg/ml min. For patient 1, the same dose of carboplatin was administered on each day of treatment, with a resultant carboplatin AUC of 3.1 mg/ml min achieved overall, i.e. 69% below the target AUC of 10 mg/ml min for this patient. For patient 2, the dose of carboplatin was increased from 16 to 45 mg/day on days 2 and 3 based on the results from pharmacokinetic analysis of samples taken on day 1 of treatment. This increase in dose led to the achievement of an overall AUC value of 9.1 mg/ml min, within 15% of the target AUC of 8 mg/ml min. This compares to a predicted total AUC of 3.6 mg/ml min, i.e. less than 50% of the target exposure, if the initial carboplatin dose, calculated from Eq. 1, had been given on each of the 3 days of treatment (Fig. 1).

Patients 3 and 4 received several courses of carboplatin treatment, with the initial dose on course 1 calculated from Eq. 1 and all subsequent doses based on the

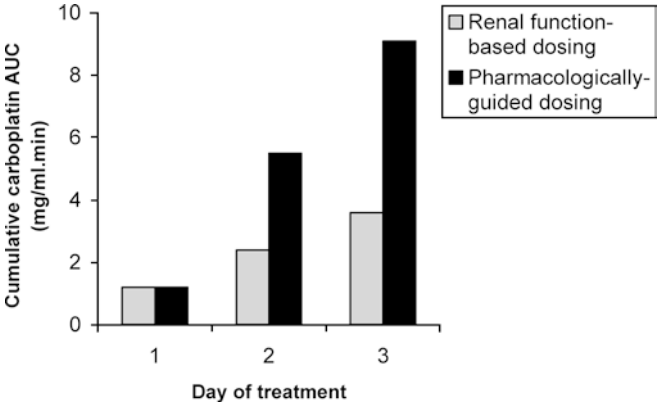

Fig. 1 Carboplatin exposure in patient 2 following pharmacologically guided dosing vs predicted exposure following renal function-based dosing. Carboplatin was administered as a 1-h infusion on each of 3 days of treatment, with the dose of drug on days 2 and 3 adjusted following pharmacokinetic analysis of samples taken on day 1. The target exposure was a total AUC of 8.0 mg/ml min over the 3 days of treatment

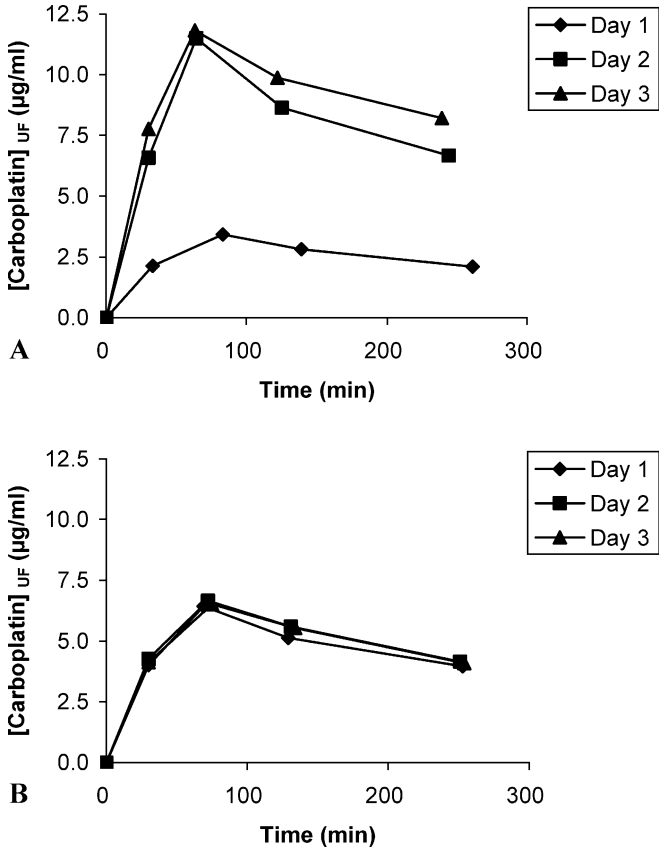

Fig. 2a, b Plasma concentrations of unbound platinum determined in patient 4 on treatment course 1 (**a**) and course 2 (**b**). Carboplatin doses administered on days 1–3 of treatment course 2 (23 mg/day) were based on the exposures observed on course 1 of treatment (15 mg on day 1; 40 mg on days 2 and 3)

observed exposure achieved following this dose. Plasma concentrations of free carboplatin determined in patient 4 on courses 1 and 2 of treatment are shown in Fig. 2.

For patient 3, a total dose of 38 mg of carboplatin was initially calculated to obtain a target AUC of 10 mg/ml min over 2 days of treatment. The actual doses of carboplatin given on courses 1, 2 and 3, following dose adjustment, were 119, 61 and 80 mg. AUC values obtained following these dose adjustments on courses 2 and 3 were 9.0 and 9.2 mg/ml min, i.e. within 10% of the target exposure in each case. The total exposure obtained on course 1 could not be determined as no samples for pharmacokinetic analysis were obtained on day 2 of treatment. If dose-adjustment based on day-1 pharmacokinetics had not been performed, estimated exposures of between 32% and 60% of the target AUC would be predicted.

Patient 4 received four courses of carboplatin, with doses on courses 2, 3 and 4 based on the exposures observed on course 1. A dose increase of 50% above the initial dose, from 15 to 23 mg/day, led to overall exposures of 8.9, 8.6 and 8.8 mg/ml min on courses 2, 3 and 4, respectively. These exposures were all within 15% of the target AUC of 10 mg/ml min.

A summary of the haematological toxicity observed in all patients is shown in Table 1. CTC grade 4 thrombocytopenia was observed in patients 2, 3 and 4, correlating with the higher carboplatin exposures achieved in these patients. Grade 4 neutropenia was observed in patients 2 and 4.

Table 3 shows actual and estimated clearance values for the four patients described in this study, in addition to data from five additional patients for whom limited pharmacokinetic data (day 1 only) were available. Actual clearance values are those determined on day 1 of course 1 of treatment for all patients, with estimated clearance values calculated using (0.36 × BW) from Eq. 1. Actual clearance values obtained for seven patients weighing <20 kg were between 27% and 260% above the estimated clearance values, whereas clearance values determined for the two larger patients, weighing 46 and 51 kg, were both within 10% of the predicted value.

Discussion

Carboplatin, in common with many other chemotherapeutic agents, exhibits a wide interpatient variation in pharmacokinetics, with threefold to fourfold variations in AUC observed following standard surface area-based dosing in children with cancer [6, 8]. As the overall exposure to carboplatin, rather than the dose of drug administered, has been shown to correlate better with clinical toxicity and response, it is clearly important that these factors are taken into consideration when treating patients. Following a study which demonstrated that renal function-based dosing results in more consistent drug exposures than dosing based on body size, this approach has now become widely accepted as the standard approach for dosing children with carboplatin chemotherapy. Furthermore, the application of pharmacokinetically guided dosing has been shown to be a feasible approach in the treatment of patients with high-dose carboplatin over several days, a scenario where drug over-exposure may lead to life-threatening toxicity [11].

In children with renal failure, paediatric carboplatin dosing equations are commonly used by inputting a GFR of zero, i.e. basing the carboplatin dose on the estimated non-renal clearance of the drug. This results in a dosing equation where the dose administered is directly proportional to body size. Importantly, Eq. 1 was derived largely from patients with normal renal function and this approach has not undergone prospective evaluation in a patient population with no renal function. Previous studies in this area have largely been individual case reports from patients with renal impairment, and there remains significant concern as to the optimal treatment of this subpopulation of patients in the clinic.

We describe here the use of pharmacokinetically guided dosing of carboplatin, following an initial dose

Table 3 Actual and estimated carboplatin clearance values in patients with bilateral nephrectomy. Actual clearance values shown are those determined on day 1 of course 1 of treatment for all patients. Estimated clearance values were calculated using (0.36 × BW) from Eq. 1. Patients 5–9 are patients previously studied for whom pharmacokinetic data were available only on the first day of treatment, including patients 5 and 6 who were discussed in a previous study by our group [1]

Patient	Body weight (kg)	Actual Cl (ml/min)	Estimated Cl (ml/min)
1	10.0	12.9	3.6
2	16.5	13.3	5.9
3	10.7	11.9	3.9
4	14.0	10.0	5.0
5	19.0	13.0	6.8
6	51.0	18.5	18.4
7	46.0	15.0	16.6
8	10.0	5.0	3.6
9	15.5	7.1	5.6

calculation based on a commonly used renal function-based dosing equation, in patients with bilateral nephrectomy. Results indicate that carboplatin dose calculation based on a child's body weight, with a GFR value of zero used in the dosing equation, leads to carboplatin exposures below the desired target AUC value. Carboplatin AUC values between 31% and 45% of target exposures were measured in four patients, for whom detailed pharmacokinetic analysis was carried out, following initial dosing based on body size. The relationship between carboplatin clearance and GFR, which was used to derive Eq. 1, was observed in patients with a normal range of renal function. The last term in this equation represents the contribution of non-renal clearance to overall elimination of carboplatin. In those patients, non-renal clearance would be as little as 20% of the total and estimation of the coefficient for body weight was imprecise. In patients with no abnormality of renal function, this is not a significant problem. However, in those with impaired or absent renal function, non-renal clearance becomes more significant and the exact relationship to body size is thus more relevant. Interestingly, the use of a fixed dose of carboplatin, as opposed to dosing based on body weight in the four patients involved in the current study would have led to the achievement of more accurate and less variable exposures. However, due to the variation in clearance values observed when looking at a larger population of anephric patients, as shown in Table 3, the use of a fixed dose of carboplatin may also lead to individual patients achieving unacceptable exposures. Interestingly, of the nine patients included in Table 3, the only two patients showing an acceptable correlation between estimated and actual clearance values were the two largest patients in this population.

The use of real-time pharmacokinetic monitoring to guide dosing within a course of carboplatin treatment resulted in exposures within 15% of the target AUC values in all patients. Encouragingly, for those patients studied on more than one course of chemotherapy, dosing based on the carboplatin exposure achieved on course 1 resulted in consistent exposures on additional courses of treatment without the need for further pharmacokinetic monitoring or dose adjustment. Clinical toxicity data from these patients indicated that the dose increases implemented were associated with significant haematological toxicity, suggesting that exposures were close to limiting levels. This level of toxicity would be expected following the chemotherapy dosing regimens being used, thus supporting the use of pharmacologically guided dosing to ensure that target exposures are being achieved in this setting. Hyperkalaemia was observed to be a side effect of chemotherapy in these anephric patients, but may have been associated equally with etoposide administration as with carboplatin chemotherapy. This was controlled initially by nebulized salbutamol, but resulted in haemodialysis being performed earlier than planned in some cases. Clearly, the monitoring of electrolyte levels in patients on chemotherapy is of significant importance and may result in some patients requiring early intervention with haemodialysis for the management of hyperkalaemia.

Carboplatin is a rare example of a chemotherapeutic drug for which knowledge of the pharmacokinetics and pharmacodynamics allows us to influence the way in which the drug is given in the clinic. Given that carboplatin clearance is known to be dependent on renal function, the use of this drug in anephric patients may be viewed with some anxiety by paediatric oncologists. However, the results of the current study demonstrate that, with appropriate pharmacokinetic monitoring and dose adjustment, an appropriate AUC can be achieved in the majority of patients. It is also apparent that the Newell formula systematically underestimates the non-renal clearance of carboplatin and further work is needed to further elucidate the relationship between non-renal clearance of carboplatin and body weight. It is essential that this knowledge is utilized efficiently and is extended into subpopulations of paediatric patients where there remain concerns about optimum carboplatin dosing strategies.

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