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Original Paper

Comparison of Methods for the Estimation of Carboplatin Pharmacokinetics in Paediatric Cancer Patients

B. Peng, A.V. Boddy, M. Cole, A.D.J. Pearson, E. Chatelut, H. Rubie and D.R. Newell

The antitumour and toxic effects of platinum drugs, in particular carboplatin, have been related to their plasma concentration and this has led to the concept of a target area under the plasma concentration–time curve (AUC) for carboplatin dosing. A formula based on renal function has been successfully applied to carboplatin dosing in adults and modified versions have also been proposed for paediatric patients. In order to monitor carboplatin AUC with maximum efficiency and minimum patient inconvenience, limited sampling strategies are desirable. A population method with Bayesian estimation is described, based on one or two samples taken following a dose of carboplatin. Population data were obtained from 22 paediatric patients treated with 200–1000 mg/m^2 carboplatin as a 60–90 min infusion. Ultrafilterable carboplatin was determined by atomic absorption spectrophotometry. A two compartment model was fitted to each data set using the Maximum Likelihood estimator of the ADAPT programme. These parameter estimates provided the prior means and covariance matrix for the Bayesian estimator using a lognormal distribution. The test data sets consisted of ultrafilterable carboplatin concentrations in 23 patients (aged 1 month–18 years) who received similar treatment. The two compartment model was fitted to data sets containing one or two points, using the Bayesian *maximum a posteriori* (MAP) estimator and an error model derived from the population error model parameters. Results from the Bayesian analysis and other methods for the estimation of AUC, including relating clearance to surface area or to renal function, were evaluated by comparing the AUC estimate with the AUC determined by model-independent analysis. Overall, the optimal sampling strategy performed better than estimates based on renal function, which had a median bias of 5% and precision of 22%. With one data point at 60 min postinfusion, the median bias and precision were 3 and 6%, respectively. Addition of a second data point at 30 min during the infusion improved the estimate slightly (median bias −2%, precision 3%). Bayesian estimation produced more reliable estimates of AUC compared to values based on renal function, which in turn was slightly better than using surface area. A technique, developed in adult patients, for estimating AUC from a measurement of 24 h total plasma platinum was comparable to estimates based on renal function, but was less reliable. The estimation of carboplatin AUC can be performed using only one or two plasma samples and Bayesian analysis. This approach is less biased and more precise than methods based on surface area, renal function or total platinum at 24 h postdose, but is probably best used in combination with dosing based on renal function.

Key words: carboplatin, pharmacokinetics, population, paediatrics
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INTRODUCTION

CARBOPLATIN IS AN analogue of cisplatin and is used in the treatment of a number of malignancies in both adults and children. For paediatric malignancies, it is a component of many treatment protocols, often in combination with etoposide or vincristine [1]. Carboplatin is less toxic than cisplatin [2, 3], in particular it does not cause nephrotoxicity and neurotoxicity, which are dose-limiting for the latter drug [4, 5]. Despite this, carboplatin still causes significant haematological toxicity which

Correspondence to A. Boddy.
B. Peng, A.V. Boddy and D.R. Newell are at the Cancer Research Unit; M. Cole and A.D.J. Pearson are at the Department of Child Health; M. Cole is also at the Department of Medical Statistics, The Medical School, University of Newcastle Upon Tyne, U.K.; E. Chatelut and H. Rubie are at the Centre Claudius Regaud, 20–24 rue du Pont Saint-Pierre, 31052 Toulouse Cedex, France.
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may limit therapy [3, 6]. Pharmacokinetic studies of carboplatin have shown that both the severity [6–9] and duration [10] of thrombocytopenia or neutropenia are related to the area under the plasma concentration–time curve (AUC) for the unbound drug. Similarly, patients with a low AUC may be less likely to experience a clinical response than patients with a high AUC [11–13], although not all authors concur with this finding [14].

The pharmacokinetics of carboplatin exhibit an appreciable degree of intersubject variability. At the same dose per metre squared, unbound carboplatin AUC can vary by 3- to 4-fold [8, 10, 14, 15]. The major route of elimination of platinum compounds is by renal excretion of unchanged drug, which accounts for up to 80% of a dose of carboplatin [16]. A definite relationship has been shown between renal function, as measured by glomerular filtration rate (GFR), and total clearance of unchanged carboplatin [3, 17]. This has led to the development of dosing equations by which the appropriate dose may be calculated for a target AUC of carboplatin or a desired degree of myelosuppression in a patient with a known renal function [3, 9, 18]. Determination of renal function is best achieved by administration of an intravenous bolus of a radiolabelled marker whose clearance approximates GFR. Suitable markers include ^{51}Cr-labelled EDTA [19] or ^{99m}Tc-labelled DTPA [20]. After administration of the marker, up to four blood samples are taken, from which the volume of distribution and elimination rate constant are determined. These are used to calculate the clearance of the marker, taken to be equal to GFR. The total clearance of unbound carboplatin is then estimated as GFR plus a constant factor to account for non-renal elimination [3, 18]. The latter route of elimination is primarily due to irreversible protein binding. Possible errors in this method, especially in the extrapolation to zero time to determine the volume of distribution of the marker, have led to the determination of GFR based on the elimination rate constant of the marker, with the volume of distribution calculated from body weight [21]. Other authors have employed a Bayesian estimation method with a physiological model of DTPA elimination to determine GFR more reliably [22]. Dosing equations based on these measures of GFR have been shown to be unbiased and reasonably precise in studies in adults [18] and, in modified form, in paediatric patients [10, 21]. Adopted prospectively, these dosing equations produce more reproducible unbound AUC values than dosing based on body size, allowing escalation of AUC levels rather than conventional dose escalation. This has allowed more consistent exposure of patients to this drug in dose-escalation studies [10, 13, 18] and the investigation of concentration–effect relationships [23]. In addition, in routine clinical practice, renal function-based dosing allows for treatment of patients with a wide range of GFR without risking either under- or overdosing.

Dosing based on estimated renal function predicts, but does not directly determine, the actual AUC achieved in an individual patient. In particular, it is error-prone due to changes in renal function between the time of determination of GFR and the administration of carboplatin. Adaptive dosing with feedback (therapeutic drug monitoring), based on determination of a full pharmacokinetic profile or on a plasma concentration at steady state, can be used to adjust the dose administered to a given patient [24]. However, this approach is very labour-intensive, both in terms of sample collection and analysis and is not suitable for short infusion administration. These general limitations have led to the development of adaptive dosing strategies for carboplatin based on limited sampling by correlating plasma AUC with the concentration in the plasma at one or two time points [25]. Such limited sampling strategies (LSS) need very careful validation, and are crucially dependent on the duration of infusion and on the timing of the critical plasma sample(s) [26]. LSS have been used successfully in the optimisation of dosing of a number of drugs including etoposide [27], 5-fluorouracil [28], vinblastine [29], amonafide [30] and ultrafilterable carboplatin [25]. An LSS for ultrafilterable carboplatin in adult patients has also been described, based on the measurement of total platinum in plasma 24 h after the dose [31]. Another method of obtaining an estimate of the pharmacokinetics of a drug in an individual is the use of a population model with an LSS and a Bayesian *maximum a posteriori* (MAP) estimator. The latter approach has been applied for a number of drugs including aminoglycoside antibiotics [32] and suramin [33]. The approach has the advantages that only one or two samples are required to estimate the AUC for an individual patient and that there is more flexibility with regard to infusion and sampling times. Bayesian estimation allows the determination of the AUC on a given course and provides an estimate of clearance which can be used to guide dosing on subsequent courses. The aim of the current study was to develop an LSS with Bayesian estimation of carboplatin pharmacokinetics in paediatric patients. The performance of this method in predicting AUC was compared to that of dosing based on surface area or renal function, and an LSS based on determination of total plasma platinum at 24 h after administration [31].

PATIENTS AND METHODS

Population data set

The patients and methods used to determine plasma ultrafilterable carboplatin in the population data set have been described previously [21]. Pharmacokinetic parameters were determined from the free platinum concentrations in 16 patients by fitting a two compartment model using the maximum likelihood (ML) estimator of the ADAPT II programme, release III (kindly supplied by BMSR, San Diego, California, U.S.A.). Pharmacokinetic parameters from these 16 patients were used to generate initial estimates of the population means and of the covariance matrix, assuming a lognormal distribution of parameters. These were used to estimate the pharmacokinetic parameters for the remaining 6 patients in whom carboplatin pharmacokinetics were best described by a one compartment model, using the MAP Bayesian estimator of the ADAPT programme. The final population means and covariance matrix were obtained by combining the parameter estimates for all 22 patients, assuming a lognormal distribution for all parameters. This was used as the population model for analysis of the validation data set.

Validation data set

Patients received carboplatin as part of established protocols, either alone or combined with etoposide, vincristine and in some cases bleomycin or cyclophosphamide. 15 patients were treated at the Royal Victoria Infirmary, Newcastle, U.K. and a further 8 at the Centre Claudius Regaud, Toulouse, France. The protocols and the pharmacokinetic study of carboplatin were all approved by the relevant local or regional Ethics Committees. Informed consent was obtained from the parents or guardians of all patients. Relevant patient information is listed in Table 1. GFR was estimated from the elimination kinetics of [^{51}CR]EDTA (Newcastle, U.K.) [19] or [^{99m}Tc]DTPA (Toulouse, France) [20].

Carboplatin was administered as a 60–90 min infusion in 5% dextrose to each patient via a peripheral cannula. Blood samples

Table 1. Patient details for validation data sets

Patient	Age (months)	Weight (kg)	Surface area (m^2)	GFR (ml/min/1.73 m^2)	Other drugs
1	64	16.9	0.75	145	V, VP, M
2	22	10.3	0.50	159	V, D, P
3	84	25.1	0.94	134	D, P
4	42	13.2	0.58	42	P
5	191	43.9	1.38	98	VP, D, R
6	14	8.9	0.41	160	V, D, P
7	221	43.5	1.40	135	V, VP, Co-p, Fl, D
8	91	24.1	0.94	177	V, VP, Fr, I, P, M
9	34	13.7	0.60	131	V, VP, P, C, M, L, Fl, I
10	58	17.6	0.72	130	V, VP
11	194	53.5	1.57	108	VP, Dic, Dih, HC, P, Th, Ac
12	15	9.2	0.44	126	PB, Ci, Ct
13	15	9.5	0.43	213	V, L, Ph, D, Bp, Fl, P
14	1	5.0	0.26	73	V, VP, CP, Fr, Al, I, M, Tu, P, vitK
15	141	34.5	1.13	107	VP, MTX(it), Th, Ct, HC, DDAVP
16	86	19.5	0.75	125	VP
17	11	8.0	0.40	111	VP
18	44	17.0	0.72	137	VP
19	107	63.0	1.61	189	None
20	61	14.0	0.62	141	VP
21	42	20.0	0.86	71	VP
22	29	14.4	0.60	129	VP
23	9	9.2	0.42	134	VP

Patients 1–15 from Newcastle, U.K. GFR by [^{51}CR]EDTA clearance. Patients 16–23 from Toulouse, France. GFR by [^{91m}Tc]DTPA clearance. Patient 15 had previously been treated with ifosfamide.
GFR, glomerular filtration rate; V, vincristine; VP, etoposide; M, morphine; D, dexamethasone; P, paracetamol; R, ranitidine; Co-p, co-proxamol; Fl, fluconazole; Fr, frusemide; I, imipenem; C, codeine; L, labetolol; Dic, diclofenac; Dih, dihydrocodeine; HC, hydrocortisone; Th, thyroxine; Ac, acyclovir; PB, phenobarbitone; Ci, ciprofloxacin; Ct, cotrimoxazole; Ph, phenytoin; Bp, benzylpenicillin; CP, cyclophosphamide; Al, allopurinol; Tu, tubocurarine; vitK, vitamin K; MTX(it), intrathecal methotrexate; DDAVP, desmopressin.

were taken via a central venous line, immediately before the start of infusion, at the middle and end of the infusion and at approximately 75, 90, 120, 180, 300 and 480 min after the start of infusion. Postinfusion sampling times were adjusted to be at uniform times (15, 30, 60 and 120 min) at the end, rather than the beginning, of the infusion. Patients treated in Toulouse, France had samples taken at 60, 90, 120, 180, 300, and 1440 min after the start of a 1 h infusion. Carboplatin was determined as free platinum by atomic absorption spectrophotometry of ultrafiltrates (Centrifree micropartition units, Amicon Ltd, Stonehouse, U.K.) prepared from each plasma sample. Details of the sample preparation and assay have been reported previously [17]. The model-independent AUC for each patient was estimated by the trapezoidal rule, with extrapolation to infinity. The terminal rate constant was determined by fitting a two compartment model using ADAPT as described previously [21].

The four most informative data points were determined using the Sample module of the ADAPT programme with D-optimality. These were found to be the points at approximately 30 min after the start of infusion, the end of infusion, at 60 min postinfusion and the last point at which free carboplatin was detected, usually approximately 480 min after the start of the infusion. Estimates of clearance, and thus of AUC, were then obtained by fitting the two compartment model with Bayesian estimation to limited data sets consisting of one of each of these four points, or data sets with all of the possible combinations of two points drawn from the four.

Using information on patient surface area, renal function, body weight and carboplatin dose, the following approaches to the estimation of carboplatin pharmacokinetics were compared:

(1) An average clearance, corrected for surface area, was obtained from the initial data set. This was used to calculate an expected AUC for the validation data set, given the dose administered and the individual surface area.
(2) Using the best model relating carboplatin clearance to patient renal function in paediatrics, carboplatin AUC was estimated from the equation

$$\text{AUC} = \frac{\text{Dose}}{\text{GFR} + (0.36 \times \text{BW})}$$

GFR is estimated as either

$$\frac{0.963}{\text{EDTA } t_{1/2}} \times (0.52 \times (843 \times \text{BW}^{0.891})) \text{ (Newcastle, U.K.)}$$

where BW is body weight in kg, or as the clearance of ^{91m}Tc-DTPA (Toulouse, France) [21].
(3) The pharmacokinetic parameters derived from the Bayesian analysis of one or two samples, as described above, were used to calculate the estimated AUC.
(4) An LSS using 24 h total platinum (Pt) and the equation

$$\text{AUC(mg/ml min)} = \frac{(24\text{ h total Pt }(\mu\text{M}) + 0.3)}{0.82}$$

was used to estimate AUC [31].

The different approaches to calculating AUC were compared to the AUC based on model-independent analysis. Bias was expressed as the per cent deviation of the estimate from the true AUC and precision as the absolute value of the deviation [34]. The distribution of bias and precision for each approach was characterised by the median, range and 25th and 75th percentiles. The utility of different methods of estimating carboplatin AUC was assessed from the magnitude of the median bias and precision.

RESULTS

The two compartment model fitted to the population data set produced a mean and covariance matrix for the four parameters as shown in Table 2, assuming a lognormal distribution. The intermediate prior matrices (n = 16) did not differ greatly from the values in the table, which included Bayesian estimation for 6 patients whose data were best fitted by a one, rather than a two compartment model.

Pharmacokinetic parameters for the validation set, obtained by fitting the same two compartment model with ML estimation to individual data sets, are given in Table 3. These were not significantly different from those obtained from the population data set [21]. As noted previously, it is not possible to fit a two compartment model to all of the data sets. For 3 of the Toulouse patients, there was insufficient data to obtain precise estimates of a two compartment model, while a one compartment model was inadequate to describe the data. Estimates of AUC and clearance (Cl) obtained by model-independent analysis of the validation data set, using the trapezoidal rule with extrapolation, have been used in the assessment of the different methods of estimating carboplatin pharmacokinetics.

Using the MAP estimator, and the prior distributions given in Table 2, it was possible to fit a two compartment model to data sets consisting of only one or two points. Comparison of median bias and precision showed that the most informative single data point was that taken 60 min after the end of the infusion. This corresponds to 120–150 min after the start of the infusion, depending on the duration of administration. The next most informative point was at 480 min after the start of the infusion (last sample taken in 16 patients), but the best combination of two data points was one halfway through the infusion (approximately 30 min after the start) and one 60 min after the end of the infusion. An alternative parameterisation of the model, with clearance proportional to individual GFR measurements, did not produce an appreciable difference in the results.

Table 2. Means and variance and covariance matrix from population data set, based on lognormal distribution

Parameter	V (l/m^2)	K_{el}/min	K_{12}/min	K_{21}/min
Mean	5.092252	0.020648	0.025259	0.018519
Variance/covariance				
V (l/m^2)	14.803	–	–	–
K_{el}/min	−0.0292	0.000182	–	–
K_{12}/min	−0.07248	0.000554	0.006631	–
K_{21}/min	−0.0135	0.0000897	0.000412	0.000118

These data form the prior means and distributions for the Bayesian estimation. V is the volume of the central compartment and K_{el}, K_{12} and K_{21} are the rate constants for elimination and distribution, respectively.

The different methods used to estimate carboplatin pharmacokinetics produced the following results:

(1) Using an average clearance value, corrected for surface area, resulted in estimates of AUC with a median bias and precision of 5 and 21%, respectively (Table 4), with a wide variation of values when compared to the true AUC (Figure 1). These data indicate that patients who would be predicted to have the same AUC based on the dose per metre squared actually had AUC values which varied 3-fold.

(2) The relationship between AUC calculated from carboplatin clearance based on renal function and the observed AUC is shown in Figure 2. Some of the variability seen in Figure 1 could be accounted for by variation in GFR, although the median bias and precision (5 and 22%, respectively) were similar to those estimated from clearance based on surface area. Interestingly, calculations based on renal function appeared to underestimate the AUC in those patients where GFR was determined by the clearance of [^{91m}Tc]DTPA.

(3) The most informative single time point for predicting AUC using the MAP estimator was found to be at 60 min after the end of the infusion, with an overall median bias of 3% and precision of 6% (Figure 3).

The addition of a second time point using the MAP estimator was investigated for the 15 patients studied at Newcastle, U.K. (Figure 4). The most informative combination of two points was one approximately halfway through the infusion added to that 60 min after the end of the infusion, the latter being the most informative single point. Median bias and precision for these patients were −2% and 3%, respectively, compared to 5% and 6% for the same group with the best single sample. This two time point analysis was not possible with the 8 patients from the other centre due to the lack of suitable sampling times.

(4) The LSS using a single determination of total platinum in plasma 24 h after the start of administration provided an estimate of AUC with a median bias of 2% (range −70 to −40%) and a median precision of 21% (range 0–70%). The distribution of both measures about the median was quite wide (Table 4) and the correlation of 24 h total plasma platinum with AUC of ultrafilterable platinum was poor in the validation data set (r^2 = 0.34) (Figure 5).

DISCUSSION

The adjustment of carboplatin dosing to take account of interindividual variation in drug clearance is based on two assumptions. The first is that the toxic and therapeutic effects of carboplatin are related to the AUC of unbound drug in plasma. This has been demonstrated in a number of studies correlating AUC with therapeutic outcome [11–13] or thrombocytopenia [6–9]. The second assumption is that the variation in carboplatin clearance among individuals is significant, and cannot be accounted for solely in terms of body surface area alone. Carboplatin clearance has been reported to vary by 3- to 4-fold in paediatric patients [10, 21] and by a similar degree in adults (reviewed in [16]), even in populations of patients with ostensibly normal renal function. However, a recent paper reported relatively little variation in carboplatin clearance in paediatric patients, suggesting that surface area-based dosing is adequate [35]. In the present study, in patients with a range of renal function (GFR 42–213 ml/min/1.73 m^2), a 3-fold variation in clearance

Table 3. Pharmacokinetic parameters for validation data set, obtained by fitting a two compartment model to full data

Patient No.	Dose (mg/m²)	AUC (mg/ml min)	Cl (ml/min/m²)	$t_{1/2}$ α (min)	$t_{1/2}$ β (min)	V_{dss} (l/m²)
1	709	7.6	91	10	76	7.8
2	560	6.0	94	30	108	5.9
3	532	4.1	129	15	100	11.8
4	388	6.9	61	–	114	5.2
5	500	8.5	60	13	90	5.8
6	585	6.4	90	18	80	7.2
7	728	8.2	87	15	107	10
8	718	6.6	108	19	83	9.3
9	750	7.2	104	7	58	6.8
10	507	6.2	84	25	88	7.9
11	592	9.9	55	31	207	8.7
12	418	5.3	79	13	91	8.4
13	512	4.7	109	20	75	7.8
14	269	3.7	51	26	195	11.8
15	558	7.1	77	18	102	8.8
16	160	2.6	72	56	420	12.7
17	125	1.6	100	23	70	9.0
18	194	3.1	ND	ND	ND	ND
19	199	2.1	117	12	67	9.1
20	97	1.5	71	44	412	10.2
21	93	4.6	ND	ND	ND	ND
22	158	1.5	121	26	70	7.9
23	143	2.4	ND	ND	ND	ND
Median	500	5.3	88	19	90	8.6
Range	93–750	1.5–9.9	51–129	7–56	58–420	5.2–12.7

ND, not determined due to insufficient data; AUC, area under plasma concentration–time curve estimated by trapezoidal rule with extrapolation to infinity; Cl, clearance; $t_{1/2}$, half-life. Cl, $t_{1/2}$ and V_{dss} are all estimated from a two compartment model.

Table 4. Bias and precision of estimators of carboplatin pharmacokinetics used to predict AUC values in paediatric patients

Method	Median	Range	25th and 75th percentile
Surface area			
Bias	5	−73 to 75	−19 and 26
Precision	21	3 to 78	16 and 33
Renal function			
Bias	5	−59 to 65	−26 and 17
Precision	22	0 to 65	13 and 30
MAP one point			
Bias	3	−28 to 26	−4 and 6
Precision	6	0 to 28	4 and 14
MAP two point (n = 15)			
Bias	−2	−19 to 3	−7 and 0
Precision	3	1 to 19	1 and 7
LSS (24 h total Pt) (n = 15)			
Bias	2	−70 to 40	−19 and 21
Precision	21	0 to 70	9 and 30

LSS, limited sampling strategies; Pt, platinum; MAP, *maximum a posteriori* estimator.

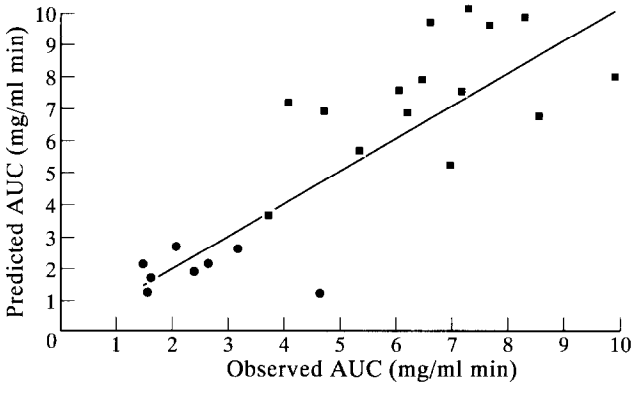

Figure 1. Estimation of AUC for the validation data set based on average clearance normalised to surface area in the initial population. Solid line is the line of identity, symbols represent estimated against true AUC value. Squares (■) are data from Newcastle, U.K. and circles (●) data from Toulouse, France.

based on model-independent analysis and corrected for body surface area was observed. Using a dosing formula based on the relationship between carboplatin clearance and GFR, much of the variability in clearance could be accounted for, and the estimated AUC was within 30% of the true value in 75% of patients. This analysis included data from two sources, one where GFR was determined by the elimination rate of [^{51}Cr]EDTA combined with some measure of total body water, and another where it was determined by the clearance of [^{91m}Tc]DTPA. Analysis of these two separate sources of data showed that the AUC estimated from [^{91m}Tc]DTPA clearance

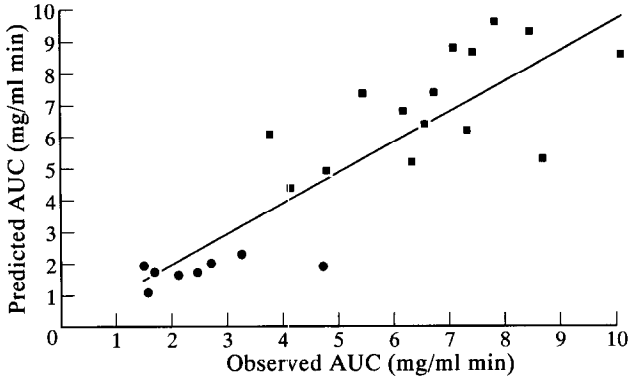

Figure 2. Estimation of AUC based on renal function. See text for explanation of formula. For explanation of symbols and lines see legend to Figure 1.

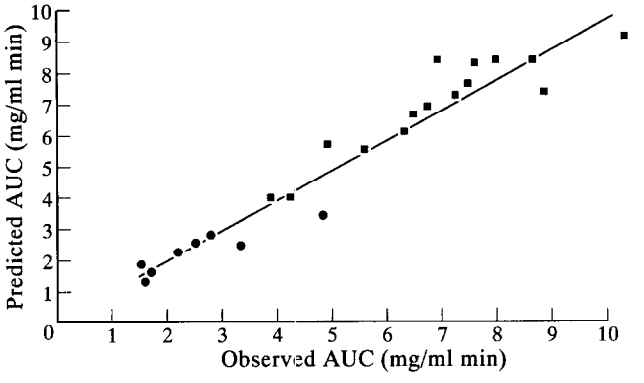

Figure 3. Estimation of AUC using a single measurement of plasma carboplatin at 60 min after the end of infusion and MAP Bayesian estimation. For explanation of symbols and lines see legend to Figure 1.

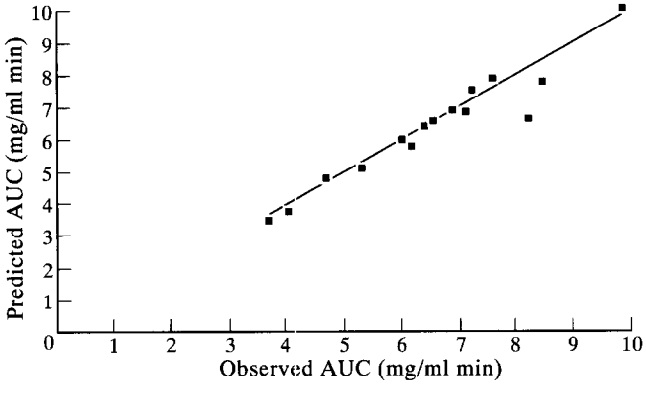

Figure 4. Estimation of AUC using two measurements of plasma carboplatin, one at 30 min after the start of infusion and one at 60 min after the end of infusion and MAP Bayesian estimation. For explanation of symbols and lines see legend to Figure 1.

tended to underestimate the true AUC, although this may have been influenced by a lower absolute value of AUC in these patients. Also, some data were from patients who had been treated with carboplatin on days immediately preceding the study day. Using [^{91m}Tc]DTPA clearance to estimate GFR has recently been shown to underestimate carboplatin clearance [36]. If a reliable measure of renal function is available for a

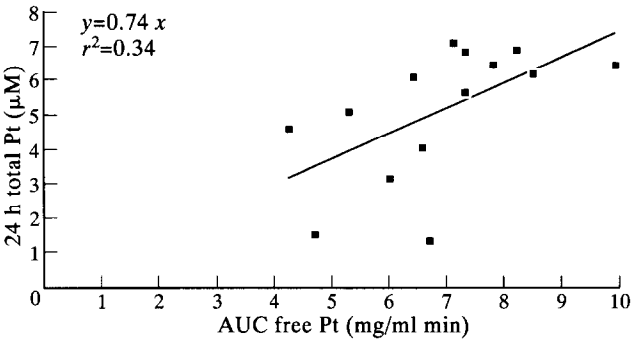

Figure 5. Correlation of total platinum (Pt) in plasma 24 h after carboplatin administration with carboplatin plasma AUC 0–24 h for the validation data set. Line is based on linear regression.

patient, particularly if renal impairment is suspected, the use of a dosing formula appears to offer an advantage over dosing based on surface area alone. This should be evaluated in a prospective study.

The use of a LSS with one point and a Bayesian analysis provides a relatively unbiased and precise estimate of AUC. The optimum sampling time is approximately 1 h after the end of the infusion, which corresponds to the inflection point between the two phases of carboplatin disposition. An additional sampling time did not greatly improve the bias or precision of the AUC estimates. The best combination of two points was one halfway through the infusion in combination with the optimal single point 60 min after the end of the infusion.

An LSS with Bayesian estimation provides a reliable estimate of AUC in patients with normal renal function. The disadvantages of this approach are that it involves the administration of an initial dose of the drug which may result in a potentially suboptimal or toxic AUC, and that access is required to plasma ultrafiltration and atomic absorption spectrophotometry equipment. Dosing based on renal function alone requires the administration of a radiolabelled marker and subsequent determination of radioactivity in plasma. Therefore, this approach can only be used by those with access to a suitable Medical Physics facility, although this is more likely to be found in a modern hospital than is the equipment for the carboplatin assay. Also, the determination of renal function based on the clearance of marker compounds is itself subject to error, as discussed previously [21]. An alternative LSS based on the correlation of AUC with one or two concentrations of unbound carboplatin measured at specified times has been proposed [25]. This approach with one sample time gave a mean bias of −4% and a mean precision of 14%. Addition of a second sample improved the bias to −2% and the precision to 9%. While this is comparable with the Bayesian approach described here, the LSS described by Sorenson and associates requires that the plasma sample be taken at a very specific time. Errors in this sampling time may lead to large errors in the estimated AUC, whereas the Bayesian approach is more flexible with regard to sampling times.

An alternative LSS for estimating the AUC of ultrafilterable platinum has been suggested which uses total plasma platinum 24 h after the start of the infusion [31]. This approach produced an estimate of AUC which was, on average, unbiased, but had poor precision for a given patient in our validation data set. The correlation of 24 h total plasma platinum with ultrafilterable platinum AUC was very poor in this patient group, possibly due to concomitant chemotherapy. In contrast, the adult patients

used to derive the initial LSS were receiving carboplatin alone [31].

In conclusion, this study confirms that AUC estimation based on renal function provides a more reproducible prediction than does surface area. A limited (one point) sampling strategy with Bayesian analysis provides an improved prediction, in terms of bias and precision, and may be used to verify the attainment of the target AUC where facilities for both approaches are available. Further refinements, such as updating the population model to take account of a growing pharmacokinetic database and the use of iterative two stage analysis, will be incorporated into future applications of this approach.

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