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Carboplatin dosing: gender bias and inaccurate estimates of glomerular filtration rate

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Abstract

The aim was to compare doses of carboplatin calculated using the Calvert formula and Chatelut formula and also to compare doses calculated using Calvert formula, modified with non-isotopic estimation of GFR, using the Cockcroft and Gault formula or the Jelliffe formula. For formulae comparison, doses were calculated to target an AUC of 7 mg/ml.min. When compared with the dose derived from the Calvert formula, the doses calculated in 122 adult cancer patients using the Chatelut formula were significantly higher for males and significantly lower for females. There was a statistically significant difference between the dose per kg calculated for males and females ($P < 0.0001$). The mean percentage difference in dose calculated with substituted measures of renal function with the Cockcroft and Gault formula and Jelliffe formula was −8% (standard deviation (S.D.) 17%) and −14% (S.D. 16%), respectively. Further prospective evaluation of the Chatelut formula is required before it can be recommended for routine clinical application.

Keywords: Carboplatin; Dosage; Glomerular filtration rate; Pharmacokinetics; Calvert formula; Chatelut formula; AUC

1. Introduction

There is increasing support for the application of dosing formulae for carboplatin based on renal function [1,2]. Carboplatin doses can be calculated from either the Chatelut formula [3] or Calvert formula [4] to achieve a targeted area under the plasma concentration versus time curve (AUC). However, there is debate as to the most appropriate and practical formula to use.

The Chatelut formula was derived from population pharmacokinetic analysis [3]. Carboplatin clearance is estimated from serum creatinine and other variables including age, height, weight and gender. The use of this formula has been supported [1,3,5,6], although it has not been formally evaluated in the randomised clinical trial setting. Local experience has suggested that the gender factor in the formula may result in biased dosing. There are no published studies that validate the Chatelut formula with an analysis by gender.

The Calvert formula was developed using glomerular filtration rate (GFR) measured by the clearance of chromium 51 ethylenediaminetetraacetic acid ([Cr^{51}]EDTA). Alternatively, the clearance of technetium 99m diethylenetriaminepentaacetic acid ([Tc^{99m}]DTPA) can be used [7–12]. However, the use of radioisotopes in the assessment of renal function is not universally available. Consequently, simpler methods of GFR estimation, using single plasma creatinine measurement to calculate creatinine clearance, have been used and substituted into the formula [13–17]. The Cockcroft and Gault formula [18] and the Jelliffe formula [19] are the most widely used. It has been demonstrated that both methods underestimate GFR [1,6,7]. As a result, the dose of carboplatin calculated may be underestimated. More recently, a population pharmacokinetic approach has been used to improve the Cockcroft and Gault equation for predicting GFR in cancer patients, but the resultant formula was not accurate enough to replace the radioisotopic methods [20].

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The aims of the study were 2-fold. Firstly, to compare the doses of carboplatin calculated using the Chatelut formula with the Calvert formula, and secondly, to also compare carboplatin doses calculated using the Calvert formula when modified with non-isotopic estimations of GFR.

2. Patients and methods

This was a retrospective study utilising data from adult patients with cancer treated at the Peter MacCallum Cancer Institute. All patients had GFR measured by [Tc^{99m}]DTPA clearance. Height, actual body weight, age, gender and serum creatinine were recorded for 122 patients. Patients were not included if they had received prior platinum chemotherapy.

2.1. Renal function estimations

GFR was determined by [Tc^{99m}]DTPA clearance [7,9]. [Tc^{99m}]DTPA was prepared 30–60 min prior to injection using fresh eluate and a current DTPA kit (Amersham International formulation). Instant thin layer chromatography was performed on all DTPA preparations approximately 30 min after reconstitution of the kit, and at the time of dose administration. Radioactivity was sampled in a Well-scintillation counter to confirm labelling efficiency of greater than 98%.

400 MBq [Tc^{99m}]DTPA was administered via a three-way tap and cannula to enable correlation with renal imaging. A 10 ml sodium chloride 0.9% flush per dose ensured no dose residue in any of the apparatus. Dose apparatus and injection site were checked for dose residue using a scintillation probe. Blood samples (10 ml) were taken at baseline and at 2, 3 and 4 h post-injection. Plasma was separated and counts obtained. The clearance of [Tc^{99m}]DTPA was calculated from a single exponential derived from the blood samples between 2 and 4 h after injection, as described by Fawdry RM and colleagues [9]. The GFR was calculated without correction for body surface area (BSA).

Serum creatinine was measured using an alkaline picrate-kinetic method, with Roche Diagnostic Hitachi 912 reagent. Creatinine clearance was then estimated using both the Cockcroft and Gault formula and the Jelliffe formula [18,19].

2.2. Formula comparisons

For formulae comparison, carboplatin doses were calculated in four ways, as if to target an AUC of 7 mg/ml.min using the Chatelut formula, the Calvert formula and also the Calvert formula modified with estimates of creatinine clearance using the Cockcroft and Gault formula and the Jelliffe formula.

Using data on GFR, serum creatinine, body weight, height, age, BSA and gender, the estimated dose of carboplatin was calculated using the following formulae:

1. Calvert formula [4]

   $$\text{Dose (mg)} = \text{AUC} \times (\text{GRF} + 25)$$

   AUC (mg/ml.min), GFR (ml/min) as clearance of [Tc^{99m}] DTPA

2. Chatelut formula [3]

   $$\text{Dose (mg)} = \text{AUC} \times (0.134 \times \text{weight}) + \frac{218 \times \text{weight} \times (1 - 0.00457 \times \text{age}) \times (1 - 0.314 \times \text{sex})}{\text{Serum creatinine} \times 100}$$

   AUC (mg/ml.min), weight (kg), age (years), sex (male = 0, female = 1), serum creatinine (mmol/l)

3. Calvert formula with creatinine clearance estimated by Cockcroft and Gault formula [18]

   $$\text{Dose (mg)} = \text{AUC} \times \left[\frac{((140 - \text{age}) \times \text{weight} \times 1.2 \times (1 - 0.15 \times \text{sex}))}{\text{Serum creatinine} \times 1000} + 25 \right]$$

   AUC (mg/ml.min), age (years), weight (kg), sex (male = 0, female = 1), serum creatinine (mmol/l)

4. Calvert formula with creatinine clearance estimated by Jelliffe formula [19]

   $$\text{Dose (mg)} = \text{AUC} \times \left[\frac{(98 - (0.8 \times (\text{age} - 20)))}{\text{serum creatinine} \times 11.3} \times \frac{\text{BSA} \times (1 - 0.1 \times \text{sex})}{1.73} + 25 \right]$$

   AUC (mg/ml.min), age (years to the nearest 10 years), sex (male = 0, female = 1), serum creatinine (mmol/l), BSA (m^2)

Pearsons correlation was used to assess relationships between doses derived from the various formulae. Analysis of differences were determined to assess bias and precision. Bias was calculated with reference to the Calvert formula. An average bias close to zero is desirable. A positive bias indicates overestimation of dose and a negative bias indicates underestimation.

A correction factor for the incorporation of each non-isotopic estimation of GFR into the Calvert formula was determined for each individual patient, by comparing the doses calculated by the Calvert and substituted

formulae. The mean of these individual factors was then calculated. Doses for individual patients were then estimated from the Calvert formula using each non-isotopic estimation of GFR and multiplied by the correction factor. Bias was then calculated with reference to the Calvert formula.

3. Results

For 122 adult oncology patients, carboplatin doses were calculated to target an AUC of 7 mg/ml.min. Specific patient demographics are detailed in Table 1. The doses calculated by applying the four formulae are detailed in Table 2.

The doses calculated using the Chatelut formula were significantly higher for males (% diff = 22%, $P < 0.001$) and significantly lower for females (%diff = −6%, $P = 0.017$) when compared with the dose derived from the Calvert formula, as detailed in Fig. 1 and Table 3. One third of male patients would have received at least 20% more than the dose determined from the Calvert formula. One quarter of female patients would have received at least 20% less than the dose determined from the Calvert formula (Fig. 2).

The difference in weight between males and females was statistically significant ($P = 0.04$). The average dose calculated using the Chatelut formula was 13.8 mg/kg for males and 11.1 mg/kg for females; this difference was also statistically significant ($P < 0.0001$).

The correlation for the GFR estimates with [Tc^{99m}]DTPA clearance was 0.67 for Cockcroft and Gault and 0.70 for Jelliffe. Both formulae significantly underestimated GFR ($P < 0.001$ and $P < 0.001$, respectively). When these non-isotopic estimates of GFR were substituted into the Calvert formula there

Table 1
Patient details and demographics (mean and range)

Demographic	All	Males	Females
Patients *n* (%)	122 (100%)	71 (58%)	51 (42%)
Age (years)	61 (21–83)	63.9 (21–82)	58.2 (32–83)
Weight (kg)	68 (42–135)	71 (45–71)	65 (42–135)
GFR [Tc^{99m}]DTPA clearance (ml/min)	87 (30–174)	89 (35–170)	85 (30–174)
Creatinine clearance: (ml/min)			
Cockcroft and Gault	75 (25–155)	77 (28–149)	72 (25–155)
Jelliffe	69 (27–119)	69 (27–119)	68 (30–109)

Table 2
Carboplatin dose (mg) calculated to target an AUC of 7 mg/ml.min using the Calvert formula, Chatelut formula and Calvert formula modified with estimations of creatinine clearance

Formula	All ($n = 122$)		Males ($n = 71$)		Females ($n = 51$)	
	Mean dose	S.D.	Mean dose	S.D.	Mean dose	S.D.
Calvert ([Tc^{99m}]DTPA)	785	199	795	201	771	196
Chatelut	850	247	956	224	707	201
Calvert (Cockcroft and Gault)	700	160	716	156	679	163
Calvert (Jelliffe)	656	125	655	126	657	124
Calvert (Cockcroft and Gault with correction factor of 1.1)	770	176	787	172	747	180
Calvert (Jelliffe with correction factor of 1.15)	754	143	753	145	765	143

S.D., standard deviation.

Table 3
Variation of the carboplatin dose (mg) calculated to target an AUC of 7 mg/ml.min using the Chatelut formula and Calvert formula modified with estimations of creatinine clearance with that calculated from the Calvert formula

Formula	All ($n = 122$)		Males ($n = 71$)		Females ($n = 51$)	
	% diff	S.D.	% diff	S.D.	% diff	S.D.
Chatelut	10	26	22	23	−6	22
Calvert (Cockcroft and Gault)	−8	17	−8	17	−9	18
Calvert (Jelliffe)	−14	16	−15	17	−12	15
Calvert (Cockcroft and Gault with correction factor of 1.1)	1	19	1	19	0	20
Calvert (Jelliffe with correction factor of 1.15)	−1	18	−2	19	1	18

% diff, % difference; S.D., standard deviation.

was a statistically significant reduction in the dose calculated ($P < 0.001$) (Figs. 3 and 4). The mean percentage difference in dose calculated with the substituted measures of renal function with Cockcroft and Gault and the Jelliffe formulae was −8% (S.D. 17) and −14% (S.D. 16), respectively (Table 3). Stratifying by gender and excluding patients with GFR <50 ml/min and >100 ml/min did not improve these results.

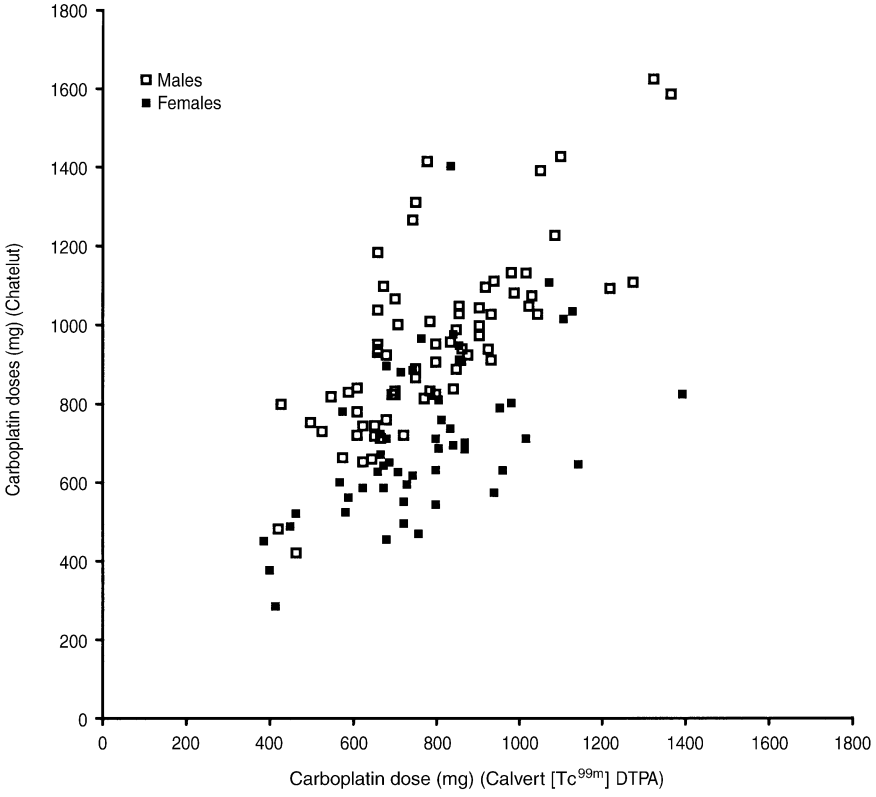

Fig. 1. Carboplatin dose determined by Chatelut formula compared with carboplatin dose determined by Calvert formula ([Tc^{99m}]DTPA).

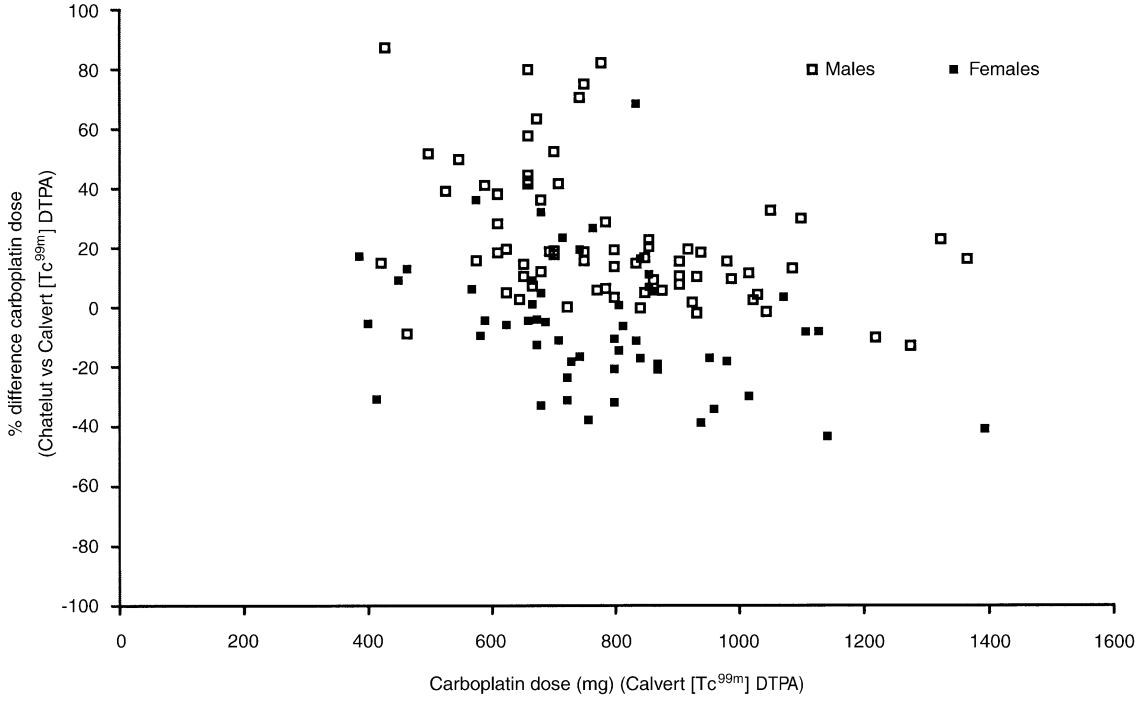

Fig. 2. Percentage difference between carboplatin dose determined by Chatelut formula and Calvert formula ([Tc^{99m}]DTPA).

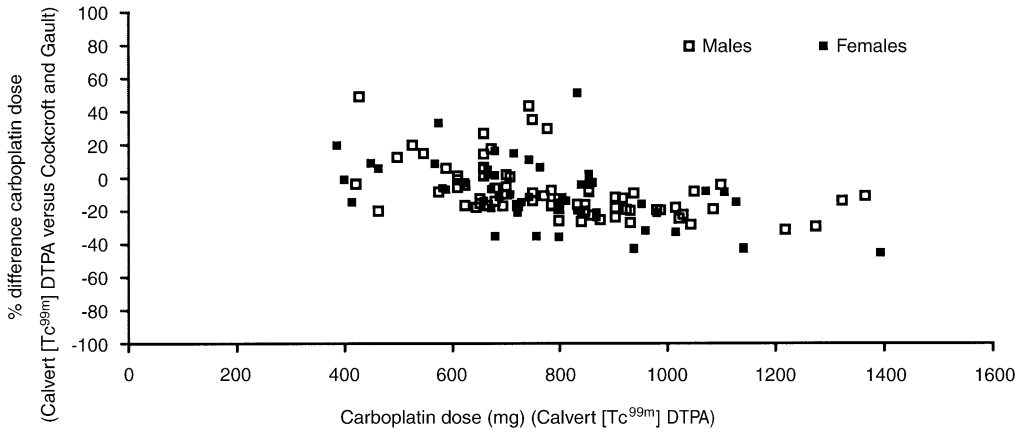

Fig. 3. Percentage difference between carboplatin dose determined by Calvert formula ([Tc^{99m}]DTPA) and substituted with creatinine clearance by Cockcroft and Gault formula.

Correction factors were determined for the Calvert formula when using the Cockcroft and Gault (1.1) or Jelliffe (1.15) formula. Incorporation of these factors improved the accuracy of the carboplatin dose calculated ($P < 0.001$ and $P < 0.001$, respectively).

4. Discussion

This study shows that the dose of carboplatin calculated to achieve a specific target AUC is very dependent on the formula applied. The Chatelut formula was derived from a population pharmacokinetic model based on nonlinear mixed effects model (NONMEM) [3]. The Chatelut formula is potentially attractive, as an accurate measurement of GFR is not required. This predictive formula was determined from analysis of the AUC on 46 cycles of carboplatin in 34 patients (23 males and 11 females). The formula was then evaluated with data from a further 36 patients (23 males and 13 females) for 43 cycles and it was concluded that this formula predicted carboplatin clearance with good precision (median absolute percentage error of 10%) and minimal bias (median percentage error of 2%). However, our results demonstrate that the Chatelut formula overestimates the dose of carboplatin for males and underestimates doses for female when compared with the Calvert formula.

To examine the influences that could confound this observation, the parameters of weight, age and serum creatinine were assessed. There was no significant difference between the mean age and serum creatinine of males and females. The average weight of females was significantly less than males. Although this is expected,

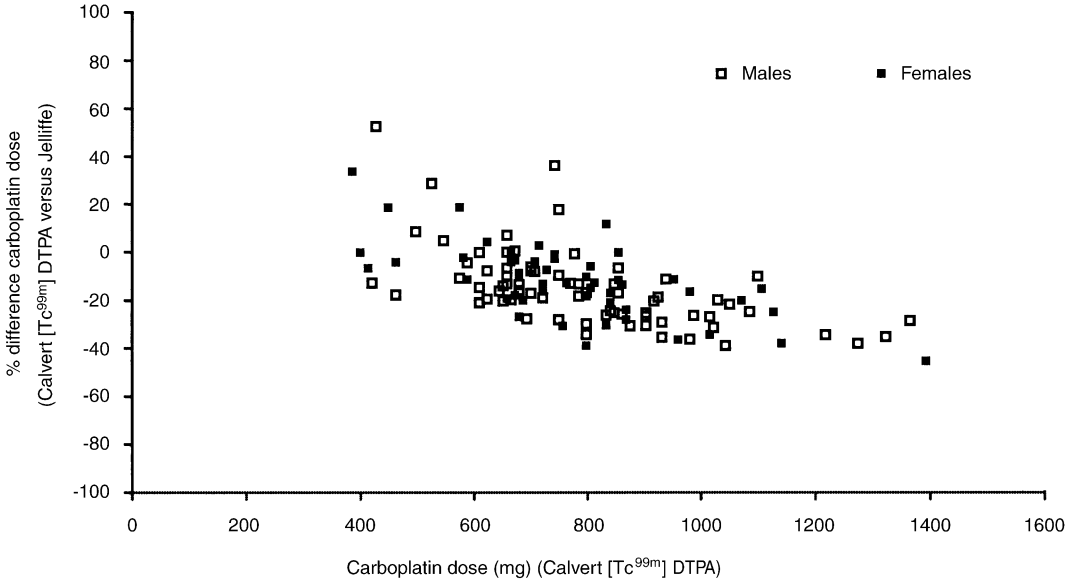

Fig. 4. Percentage difference between carboplatin dose determined by Calvert formula ([Tc^{99m}]DTPA) and substituted with creatinine clearance by Jelliffe formula.

it does not explain the magnitude of the dose differences estimated by the Chatelut formula. There was a statistically significant difference between the mg dose per kg calculated for males compared with females. Males on average weighed 9% greater, but would have received approximately 25% more carboplatin per kg than females.

The parameters required for dosage calculation using the Chatelut formula include weight, age, gender and serum creatinine. Gender is factored into the component of the formula that estimates renal carboplatin clearance. The estimate of renal carboplatin clearance for females is calculated at 31.4% less than that of males. Intuitively this would seem a very large reduction, as the gender factor in the Cockcroft and Gault formula and the Jelliffe formula is 15 and 10%, respectively. This was confirmed in this study in that the Chatelut formula underestimated the dose of carboplatin for female patients. One quarter of female patients would receive at least 20% less than the dose determined from the Calvert formula. Validation of the Chatelut formula for gender was not performed in the original study and has not been published subsequently. We are unaware that any other comparison of gender differences have been explored in the validation of any of the carboplatin dosing formulae, including the Calvert formula, this appears to be an area that requires further evaluation.

The Calvert formula has been shown to be a superior method of dosing carboplatin than the traditional BSA method [1,2]. The primary impediment to its application has been the requirement for an accurate measurement of GFR. The original work on dosing with this formula utilised [Cr^{51}]EDTA clearance [4]. An accurate measurement of GFR is possible by measuring the clearance of either radiolabelled [Tc^{99m}]DTPA or [Cr^{51}]EDTA [7–12]. The use of [Tc^{99m}]DTPA is preferred in some facilities because of greater convenience and reduced cost. The precision of these estimates depends on the radiopharmaceutical and the method used to calculate clearance. Local factors relating to the source and extent of protein binding of [Tc^{99m}]DTPA can also influence the accuracy of results. Some investigators have found [Tc^{99m}]DTPA clearance unsuitable for the prediction of carboplatin pharmacokinetics [3]. However, this has been as a result of determining the GFR by calculation of renal uptake of the radiopharmaceutical rather than by direct determination of blood clearance [3]. Chatelut and colleagues measured GFR by the method proposed by Gates [21] which has been shown to be less accurate than direct measurement [9,22]. The accuracy of the determination of GFR in our study is supported by the following factors. The methodology utilised in this study, with [Tc^{99m}]DTPA clearance determined by absolute blood clearance from repeated blood sampling, has been shown to be accurate [11]. This method has also been simultaneously compared with [Cr^{51}]EDTA clearance at this centre and shown to be accurate in that clearances of both these agents were closely correlated ($r = 0.98$), the regression line having a slope of near unity (1.02) and the intercept being close to zero [7]. The methodology was replicated in the same laboratory using the same source of radiopharmaceutical as for this study.

The routine availability of isotopic methods of accurately determining GFR is not possible in many centres. Consequently, more indirect and less complicated methods have been utilised for estimating creatinine clearance including 24-h urinary creatinine clearance and formulae based on single plasma creatinine levels. However, 24-h urinary creatinine clearance has been shown to be unreliable [7,23,24]. Recently, Wright and colleagues presented, in abstract form, another formula for estimating renal function from serum creatinine, which may be less biased and more precise than other formula-based methods [25]. However, this requires prospective evaluation before it is incorporated into routine practice. Substitution of creatinine clearance estimates of GFR from the Cockcroft and Gault formula and the Jelliffe formula into the Calvert formula has become routine practice. In this study, the mean percentage difference in dose calculated with these substituted measures of renal function was significantly less. This was a direct result of the poor correlation between the estimates of renal function. The correlation remained poor despite removing the low and high range GFR.

These results support the application of a correction factor to the Calvert formula when creatinine clearance estimates are substituted for actual GFR measurements. Substituting the Cockcroft and Gault estimation of GFR into the Calvert formula underestimates the dose of carboplatin with almost 20% of patients receiving at least 20% less than the dose determined from the Calvert formula. Similarly, when the Jelliffe estimate is used, 34% of patients would receive at least 20% less than the dose determined from the Calvert formula using the isotopic estimation of GFR. These results are consistent with findings in other studies [5,26,27]. Application of correction factors determined for the Calvert formula when using the Cockcroft and Gault and the Jelliffe estimations of creatinine clearance resulted in improved accuracy of the carboplatin dose calculated and now require prospective evaluation.

It has been shown that the method of serum creatinine measurement can influence the accuracy of the estimation of carboplatin dose. This variability has been quoted to be up to 20% when determined by the Jaffe reaction. However, this is very dependent on the specific methodology utilised [6,28]. The methodology used in this laboratory for this study has been validated against enzymatic methods and showed less than a 1.2%

variability indicating minimal influence on the doses calculated. Additional corrections may be required when methods of creatinine measurement are used that are less accurate than in this study.

Recently, the development of Bayesian techniques for predicting carboplatin exposure have been proposed to improve the accuracy of dosing [29,30]. The accuracy of these methods need further validation in the prospective setting. In addition, the sampling and analysis requirements will be impediments to the widespread application into routine clinical practice.

Our results question the validity of the Chatelut formula in accurately estimating the dose of carboplatin when compared with the Calvert formula. To our knowledge, this is the first time that the potential inaccuracies relating to gender differences have been demonstrated. The most recent study to further support targeted AUC estimation of carboplatin dose, reviewed 505 patients treated with carboplatin and demonstrated that the Calvert–Cockcroft and Gault formula provides, for a given patient, an AUC superior to the Chatelut formula [2]. This observation has also been demonstrated by others [31]. In the light of the results of our work, we cannot recommend the routine application of the Chatelut formula until further prospective evaluation is completed. The most appropriate method of dosing carboplatin is the Calvert formula using either [Cr^{51}]EDTA or [Tc^{99m}]DTPA clearance. When an isotopic measurement of GFR is not possible, incorporation of Cockcroft and Gault formula or Jelliffe formula estimation of creatinine clearance can be applied. However, the formula should be modified to account for the underestimation of renal clearance of carboplatin.

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