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ORIGINAL ARTICLE

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Prospective evaluation of carboplatin AUC dosing in patients with a BMI ≥27 or Cachexia

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Abstract When determining the carboplatin dosage from the Calvert formula, there are a lack of data when evaluating patients with cachexia or body mass index (BMI)≥27. If the Cockcroft and Gault (C-G) creatinine clearance (CrCl) equation is utilized and substituted for glomerular filtration rate in the Calvert formula, the chance for inaccurate dosing occurs especially in these populations. Therefore, the purpose of this study is to evaluate and compare the target carboplatin area under the concentration (AUC) with the actual AUC achieved in cachectic or BMI≥27 patients. In a prospective manner, we evaluated 19 patients with a BMI≥27 and nine cachectic patients. In the C-G equation to determine creatinine clearance, the adjusted body weight was used for BMI≥27 patients and serum creatinine value of 70.7 μM (0.8 mg/dl) for the cachectic patients. The carboplatin dose was calculated, administered to the patients, and subsequent carboplatin blood samples were obtained for pharmacokinetic determination. Once the AUC was determined, the results were compared with the expected outcomes from the modified C-G CrCl equation for the Calvert formula, Chatelut and Bénézet equations. The results demonstrated that the modified C-G CrCl equation for the Calvert formula had less bias and more precision than using actual weight in the C-G CrCl equation or using the Chatelut and Bénézet equations. Using the actual weight in overweight and especially obese patients and using a serum creatinine < 70.7 μM in cachectic patients will lead to overestimation of the carboplatin clearance and thus AUC.

Keywords Pharmacokinetics · Carboplatin · AUC · Overweight · Obese · Cachexia

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Introduction

The use of the Calvert formula [2] (dose = target AUC× (GFR +25) for the carboplatin dose calculation is widely utilized; however, it does have limitations in clinical practice. The determination of glomerular filtration rate (GFR) by measuring the clearance of chromium 51 ethylenediaminetetraacetic acid is not available to all clinicians and is costly. Therefore, many have used the Cockcroft-Gault (C-G) [4] equation to estimate creatinine clearance (CrCl) which is substituted for GFR in Calvert's formula. Since Cr is both filtered by the glomeruli and secreted by the tubules, CrCl theoretically exceeds GFR. Even with this difference, some studies have utilized and evaluated the C-G CrCl equation instead of GFR to calculate the carboplatin dose [8, 9, 11, 14, 19, 20, 27]. The C-G equation has two variables (weight and creatinine) that are dependent on the patient's body composition. Therefore, overweight or cachectic patients with low serum creatinine levels have a high risk of an inaccurate carboplatin dose determination. There are no prospective studies for evaluating the Calvert formula in obese or cachectic patients. There is clinical evidence that using actual body weight in the C-G CrCl calculation and for the Calvert GFR can produce a higher than expected carboplatin area under the concentration–time curve (AUC) [5]. The purpose of this evaluation was to determine if the modified C-G equation could accurately predict the actual AUC achieved in BMI≥27 or cachectic patients.

Methods

The investigational review board reviewed and approved the prospective protocols. Adult patients scheduled to receive a carboplatin 1-h infusion were screened for inclusion into either the cachectic or BMI≥27 trials. In the cachectic study, patients were identified if they had a serum creatinine <70.7 μM, a ≥5% weight loss over 6-month period, serum albumin of <34 g/l, and a BMI <27. In the BMI≥27 trial, patients were identified if they had absence of ascites and a serum creatinine ≥61.9 μM. Patients were weighed and height measured on the treatment day and a serum creatinine and albumin (for cachectic trial) were drawn within 30 days of enrollment. The serum creatinine method employs a modified kinetic Jaffé reaction by using the alkaline picrate method with Dade Dimension RxL reagent.

Modified Calvert formula for BMI≥27 patients

The carboplatin dose was calculated as follows:

1. Calculate ideal body weight

$$\begin{aligned}\text{Weight (kg) for males} &= 50\,\text{kg} \\ &+ (\text{number of cm over } 152.5\,\text{cm in height} \times 0.91) \\ \text{Weight (kg) for females} &= 45.5\,\text{kg} \\ &+ (\text{number of cm over } 152.5\,\text{cm in height} \times 0.91)\end{aligned}$$

2. Calculate adjusted body weight (AdjBW)

$$\begin{aligned}\text{Adjusted body weight (kg)} &= \text{Ideal body weight} \\ &+ 0.4\,(\text{actual body weight} \\ &- \text{ideal body weight})\end{aligned}$$

3. Calculate creatinine clearance (CrCl) using adjusted C-G equation

$$\text{CrCl} = \frac{((140 - \text{age}) \times \text{AdjBW (kg)} \times 1.23)}{\text{serum creatinine } (\mu\text{M})} \times 0.85 \quad \text{for females}$$

4. Calculate carboplatin dose by Calvert formula, mg = AUC (GFR + 25) (substitute CrCl for GFR in equation)
5. The dose of carboplatin was administered to the patient and pharmacokinetic levels were obtained.
6. Once carboplatin clearance was determined, this formula was recalculated using ideal body weight instead of adjusted body weight. The dose was recorded and subsequent AUC predicted based on the patient's actual carboplatin clearance.

Modified Calvert formula for cachectic patients

1. Use serum creatinine of 70.7 μM in the CrCl calculation

$$\text{CrCl} = \frac{((140 - \text{age}) \times \text{weight (kg)} \times 1.23)}{\text{serum creatinine } (\mu\text{M})} \times 0.85 \quad \text{for females}$$

2. Calculate carboplatin dose by Calvert formula (substitute CrCl for GFR in equation)
3. Carboplatin dose in mg = AUC×(GFR + 25)
4. The dose of carboplatin was administered to the patient and pharmacokinetic levels were obtained
5. Once the actual carboplatin clearance was determined, it was compared to the estimated results from the Chatelut equations.

The Bénézet equation [1] for obese patients was used to predict the carboplatin clearance.

1. Calculate carboplatin clearance

$$\text{Carboplatin Cl (ml/min)} = 0.134 + \frac{218 \times (1 - 0.00457 \times \text{age}) \times (1 - 0.314 \times \text{sex})}{\text{serum creatinine } (\mu\text{M})}$$

Sex: males = 0; females = 1

2. Multiply above sum: (ideal body weight + 0.512 (actual weight − ideal weight)

$$\text{Ideal weight (kg)} = \text{height in cm} - 100 - \frac{(\text{height in cm} - 150)}{4(\text{males}) \text{ or } 2(\text{females})}$$

3. Calculate the carboplatin dose if the Bénézet equation would have been used:

$$\text{Dose} = \text{Bénézet carboplatin clearance} \times \text{target AUC}$$

4. Calculate the anticipated AUC utilizing the actual carboplatin clearance:

$$\text{Anticipated AUC} = \frac{\text{Bénézet dose}}{\text{actual carboplatin clearance}}$$

Chatelut equation [3] was used for the cachectic patients.

1. Calculated carboplatin clearance

$$\text{Carboplatin Cl (ml/min)} = 0.134 \times \text{weight (kg)} + \frac{218 \times \text{kg} \times (1 - 0.00457 \times \text{age}) \times (1 - 0.314 \times \text{sex})}{\text{serum creatinine } (\mu\text{M})}$$

Sex: males = 0; females = 1

2. Calculate the carboplatin dose if the Chatelut equation would have been used:

$$\text{Dose} = \text{Bénézet carboplatin clearance} \times \text{target AUC}$$

3. Calculate the anticipated AUC utilizing the actual carboplatin clearance:

$$\text{Anticipated AUC} = \frac{\text{Chatelut dose}}{\text{actual carboplatin clearance}}$$

Bias was measured using the mean prediction error (MPE) with the standard error of mean. The 95% confidence interval was also calculated for the MPE. Precision was measured by using the root-mean-squared prediction error (RMSE) [22].

Pharmacokinetic assessment

For the determination of carboplatin (free platinum, UF-PT) pharmacokinetic parameters, a limiting sampling strategy was utilized and modeling was evaluated using a 1-compartment model, incorporating Bayesian estimation as previously described elsewhere [13]. The population pharmacokinetic parameters used to formulate the Bayesian model were as follows: mean volume of distribution, 14.1 l/m2 (coefficient of variation, 60%) and mean elimination rate, ke, 0.22 h −1 (coefficient of variation, 55%). Pharmacokinetic modeling was performed using ADAPT II software version 4.0.

Blood samples (5 ml in heparinized collection tubes) were obtained at 0.5, 1, 1.5, and 6 h after the beginning of the carboplatin 1-h infusion. All of the samples were centrifuged at 3,000 rpm for 15 min at 4°C immediately after collection, and the resulting plasmas were further separated and plasma ultrafiltrate were stored at −20°C until analyses. Concentrations of carboplatin in plasma ultrafiltrate samples obtained during carboplatin treatment were analyzed for the presence of platinum at M.D. Anderson Cancer Center, using validated flameless atomic absorption spectroscopy (FAAS) (SPECTRAA-300; Varian, Sugar Land, TX, USA) with a graphite tube atomizer assay as described by Madden et al. [16, 25] with minor modifications.

Briefly, standards, controls, and samples were injected at 20 µl into the graphite tube at a temperature of 25°C. The furnace temperature was increased from 25°C to 1,300°C in five steps over 1.5 min, held at 1,300°C (ashing) for 2 min, raised to 2,700°C over 1 min (atomization), and held at for 5 s. The argon gas flow was 3 l/min. In addition, the hollow cathode lamp current was 10 mA, and the spectral bandwidth was 0.7 nm at a monochromator wavelength of 265.9 nm with a signal integration time of 5 s and background correction with a deuterium lamp. A linear standard curve covering the platinum range of 50–400 ng/ml was run at the start of each assay day and after each change to a new graphite tube. Plasma ultrafiltrate samples were diluted in 0.1 N HCl; all samples were diluted to achieve concentrations within the linear portion of the standard curve. Sample concentrations were determined by comparing sample peak concentrations with those of external standards using linear least-squares regression analysis. The FASS was operated under conditions that maximized sensitivity. This method detected elemental platinum only but did not indicate the chemical form of the metal. Thus, all of the values calculated from the calibration curve were converted to an equal molar amount of carboplatin.

Results

A total of 19 patients participated in the BMI≥27 trial and 9 patients in the cachectic trial. Patient demographic data are described in Table 1. The median BMI was 30.7 in the BMI≥27 trial compared to 22.9 in the cachectic trial. In both populations, the median target carboplatin AUC was 5 (range, 2–7). The pharmacokinetic parameters between the groups were similar (Table 2).

For the BMI ≥ 27 cohort, the use of the adjusted body weight for determining the CrCl is more precise compared with the estimated AUC achieved with actual weight (Table 3). The RMSE% or precision was found to be 21.1% for adjusted body weight, 32.9% for actual weight, and 39.1% for the Bénézet obese equation. The

Table 1

Demographics	BMI≥27	Cachexia
Male/female, no. of patients	11/8	5/4
Age (years) median (range)	61 (49–75)	67 (44–73)
Weight (kg) median (range)	97 (73.6–123.2)	68.2 (47.7–75)
BMI (kg/m^2) median (range)	30.7 (27.6–48.1)	22.9 (18.6–25.3)
Serum creatinine (µM), median (range)	79.6 (61.9–185.6)	53.0 (35.4–61.9)
Albumin (g/dl), median (range)	N/A	26 (19–33)
Weight loss over 6 months (%)	N/A	11.2 (6.8–25.6)
Primary tumor site, no. of patients		
Lung	9	7
Gynecologic	6	1
Lymphoma	2	–
Unknown primary	2	–
Breast	–	1
Concurrent therapies		
Paclitaxel	10	5
Etoposide	3	3
Gemcitabine	2	1
Ifosfamide/mesna/etoposide	2	
Irinotecan	1	
Radiation	1	

Table 2 Carboplatin pharmacokinetic parameters

	BMI≥27 ($n=19$) Median (range)	Cachexia ($n=9$) Median (range)
T 1/2 (h)	1.8 (1.2–3.2)	1.8 (1.2–2.4)
CL (ml/min)	100.9 (53.2–152.8)	100.8 (63.9–136.8)
Vc (l)	16.2 (13.4–27.8)	17.1 (9.7–33.0)

Table 3 Results: observed and estimated carboplatin AUCs

	AUC, mean ± SD	MPE ± SE (%)	95% CI	RMSE (%)
BMI≥27 patients ($n=19$)				
Target AUC	5.2 ± 1.2			
Actual AUC achieved with adjusted weight	5.7 ± 1.7	7.7 ± 4.6	−2.0 to 17.5	21.1
Estimated AUC if IBW is used	5.0 ± 1.5	−4.3 ± 4.5	−13.7 to 5.1	19.4
Estimated AUC if actual weight is used	6.7 ± 2.1	24.0 ± 5.3	12.9 to 35.2	32.9
Estimated AUC if Bénézet obese equation is used	7.2 ± 2.4	30.0 ± 5.9	17.7 to 42.4	39.1
BMI≥30 patients only ($n=11$ of 19)				
Target AUC	5.3 ± 0.7			
Actual AUC achieved with adjusted weight	6.0 ± 1.1	10.6 ± 4.5	0.7 to 20.6	17.6
Estimated AUC if IBW is used	5.1 ± 0.9	−4.9 ± 4.2	−14.2 to 4.3	14.0
Estimated AUC if actual weight is used	7.3 ± 1.6	31.0 ± 5.6	18.5 to 43.4	35.6
Estimated AUC if Bénézet equation is used	7.5 ± 1.9	31.9 ± 7.8	14.5 to 49.2	40.3
BMI ≥ 27 to < 30 patients only (n = 8 of 19)				
Target AUC	4.9 ± 1.8			
Actual AUC achieved with adjusted weight	5.3 ± 2.3	3.7 ± 9.4	−18.4 to 25.9	25.1
Estimated AUC if IBW is used	4.9 ± 2.2	−3.5 ± 9.4	−25.6 to 18.7	25.0
Estimated AUC if actual weight is used	5.9 ± 2.6	14.5 ± 9.4	−7.7 to 36.8	28.8
Estimated AUC if Bénézet equation is used	6.7 ± 3.0	27.5 ± 9.5	5.0 to 50.0	37.3
Cachectic patients (n = 9)				
Target AUC	5.1 ± 1.5			
Actual AUC achieved with 70.7 μM as default creatinine value	5.6 ± 2.1	5.2 ± 6.4	−9.6 to 19.9	18.8
Estimated AUC if actual creatinine	7.8 ± 3.3	37.2 ± 8.2	18.4 to 56.0	43.8
Estimated AUC if Chatelut equation with actual creatinine	10.4 ± 5.1	63.4 ± 10.4	39.5 to 87.2	69.8

Bénézet obese equation was the least precise of the three methods. In terms of bias, the adjusted body weight equation overestimated the AUC by less than 8% (MPE 7.7%, 95% CI, −0.2 to 17.5) versus underestimating less than 5% if ideal body weight was utilized (MPE –4.3%, 95% CI, −13.7 to 5.1). Both of these equations had significantly less bias than the use of the actual weight equation (MPE 24%, 95% CI, 12.9–35.2) or the use of the Bénézet obese equation (MPE 30%, 95% CI, 17.7–42.4).

The BMI≥27 group was separated in Table 3 to evaluate the overweight patients (BMI < 30) and obese patients (BMI≥30). The obese patients using the adjusted body weight (RMSE 17.7%) or ideal body weight (RMSE 14%) equations had more precision versus the Bénézet (RMSE 40.3%) or actual body weight (RMSE 35.6%) equation. In terms of bias, the ideal body weight estimation of AUC had less bias (MPE−4.9%, 95% CI, −14.2 to 4.3) compared to adjusted body weight (MPE 10.6%, 95% CI, 0.7–20.6). The use of actual weight (MPE 31.0%, 95% CI, 18.5–43.4) or the Bénézet (MPE 31.9%, 95% CI, 14.5–49.2) equations were associated with significant bias. For the overweight patient group, the three weight groups had similar precision (RMSE range 25.0 to 28.8%) unlike the Bénézet equation (RMSE 37.3%).

The cachectic cohort of patients using the adjusted creatinine value in the C-G equation in the modified Calvert formula exhibited less bias (MPE 5.2%, 95% CI, −9.6 to 19.9) compared to the unadjusted serum creatinine equation (MPE 37.2%, 95% CI, 18.4–56.0) or the Chatelut formula (MPE 63.4%, 95%CI, 39.5–87.2). In terms of precision, the adjusted creatinine value equation had more precision (RMSE 18.8%) compared to unadjusted creatinine equation (RMSE 43.8%) and the Chatelut equation (RMSE 69.8%).

Discussion

There are no prospective studies evaluating the Calvert formula in obese or cachectic patients. Hutson and colleagues evaluated the C-G equation and the Calvert formula in 59 patients with an average BMI of 26.6 (range 17.9–40.4) [10]. Their conclusion from this retrospective study was that actual body weight has less bias than ideal or adjusted body weights; therefore, actual body weight should be used in the C-G equation. However, this conclusion was based on data containing patients who were not overweight (BMI < 25). Since the majority of patients were not obese (BMI≥30), their conclusions should be not generalized to this population [10]. Our data in Table 3 suggest that the use of actual weight should not be utilized in obese patients; however, the magnitude of the difference between actual and

predicted AUC is reduced in overweight patients (BMI < 30).

Historically, there has been a debate on the proper medication dosage in obese individuals. With the agents being dosed by weight, there are concerns about the safety and efficacy of certain agents in obese patients. Unfortunately, there is a paucity of data that addresses this issue. In 2004, an abstract supported the use of the adjusted body weight equation for patients receiving high-dose etoposide [23]. The authors noted that using actual body weight increased skin toxicity and a higher early death rate. The use of the adjusted body weight provided a better safety profile without loss of outcome [23].

The adjusted body weight equation has primarily been used to calculate aminoglycoside and other antibiotics doses in obese patients [29]. In this equation, the "0.4" value is termed the "dosing weight correcting factor" (DWCF). The DWCF is dependent on the agent's ability to distribute through adipose tissue. Typically, the higher the DWCF the more likely the agent will be well distributed throughout the system. Carboplatin is hydrophilic in nature and therefore should not have a high DWCF [26]. It is unknown as to which correction factor would be ideal. For obese patients (BMI ≥30), our data suggest that the ideal body weight equation has less bias compared to adjusted weight. For example, if the DWCF is lowered to "0.2", it will certainly improve the bias; however it will not improve the precision.

There is clinical evidence that using actual body weight in the C-G CrCl calculation and substituted for the Calvert GFR can produce a higher than expected carboplatin AUC [5]. A published case describes a morbidly obese patient (BMI 47) receiving chemotherapy containing carboplatin, targeting a total AUC of 12 infused over a 4-day period. The patient's actual weight was utilized in the C-G CrCl equation, which produced an actual AUC of 25.5 instead of the target AUC of 12. This value would have been even higher, but the authors ended the infusion early after they discovered the elevated AUC on the third day of the 4-day carboplatin regimen.

If the serum creatinine value is not reflective of the patient's true CrCl and is thereby inserted into the C-G CrCl equation, it is intuitive that the result will be erroneous. This is especially worrisome if the patient's creatinine is low and if this value is used in the C-G CrCl equation. This will invariably influence a higher than expected CrCl. Thus, if this CrCl is utilized within the Calvert formula, the carboplatin dosage will be higher than predicted. There are several trials evaluating the effect of rounding-up the creatinine value in order to improve the precision and bias of the C-G equation. In the literature, these correction values have been listed from 61.9 μM to 88.4 μM (0.7–1.0 mg/dl), with improved results compared with using the non-corrected creatinine value to estimate the actual CrCl [7, 18, 21, 24]. We cautiously chose the value 70.7 μM since the possibilities that 61.9 μM may produce elevated AUCs and the 88.4 μM will create suboptimal AUCs. As the data demonstrated, the correction value of 70.7 μM has less bias and more precision compared with using the actual creatinine. However, by increasing the corrected value to 80 μM or 90 μM, it will improve the bias in our study; however, it is unknown if this trend will continue in a larger sample size.

In our trial, we utilized the modified Jaffé reaction to measure the serum creatinine concentrations. However, this method has been shown to produce variability when used in other equations such as Chatelut, which was developed using enzymatic creatinine amidohydrolase assay. Jaudon et al. [12] evaluated 244 samples to ascertain the impact of switching from an enzymatic assay to the colorimetric Jaffé method when using the Chatelut equation. On average, the Jaffé method overestimated the serum creatinine level by 13.9% compared to the enzymatic assay. Therefore, the investigators developed a correction value when using the Jaffé method for measuring creatinine to be used in the Chatelut or Bénézet equations. Serum creatinine μM = (Jaffé creatinine μM − 1.6)/1.08.

Léger et al. [15] evaluated the impact of the different serum creatinine assay measurements on the carboplatin AUC dosing strategies. In this study, the investigators utilized the correction equation as above to evaluate the relationship between corrected and uncorrected Jaffé creatinine methods. The bias (95% CI) was −7.4% (−15.4 to 0.6) for the uncorrected serum creatinine compared to a bias of 1.1% (−7.6 to 9.7) in the corrected group. The authors stated that an 8% dosage increase would be necessary if the Jaffé method was utilized in Chatelut equations. However, in our study groups, the Chatelut and Bénézet equations were already heavily biased with values of MPE 63.4% (95% CI, 39.5–87.2) and MPE 30% (95% CI, 17.7–42.4), respectively. Therefore, the suggested 8% dosage increase suggested by Léger and colleagues would not be necessary in our obese and cachectic populations.

There are several questions still present on how to dose patients who do not meet our study criteria. This study did not address the following questions: how do you adjust the patients who are obese but have a serum creatinine < 61.9 μM. In addition, for those patients who are not cachectic and have a serum creatinine < 70.7 μM, do you adjust the creatinine value to 70.7 μM? In our current practice, we do correct the serum creatinine value up to 70.7 μM (0.8 mg/dl) in all adult patients.

It is imperative to remember that all of these equations included in this study and those that have been proposed in the literature are all error-prone [6, 17, 28]. Whether it is a problem with the creatinine assay, patient weight, or gender bias, all proposed equations have some degree of bias and lack of precision. It is important to understand the limitations of these equations and adjust the variables as needed. In addition, it is well known that whichever equation is being utilized, it will

certainly be more accurate than using the body surface area dosing method.

Even though the patient numbers in our study populations are small, preliminary conclusions may be drawn from our experience. For patients who are obese, the use of ideal or adjusted body weight in the C-G CrCl equation and substituted for GFR in the Calvert formula will produce appropriate carboplatin AUCs. In addition, the use of actual weights in the C-G CrCl equation and substituted for GFR in the Calvert formula or the use of the Bénézet obese equation will produce higher than expected AUCs. For cachectic patients, the use of an adjusted creatinine to 70.7 μM (0.8 mg/dl) will produce greater precision and less bias compared with using actual creatinine values or the use of the Chatelut equation. The use of the actual creatinine values in cachectic patients will lead to substantial overestimation of clearance and dose.

In conclusion, the results of this prospective trial demonstrate that the modified Calvert equations exhibited less bias and more precision compared to the Bénézet and Chatelut formulae in our overweight, obese, or cachectic populations. If the C-G equation is utilized and substituted for GFR in the Calvert formula, proper weight or creatinine adjustments are necessary to avoid overestimating the target carboplatin AUC. The Bénézet obese equation and Chatelut equation in cachectic patients are not recommended because of the significant risk of AUC overestimation.

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