GYNECOLOGY

Correlation of Creatinine Clearance Calculated by Cockcroft & Gault Equation and 24-hour Urine Collection in Gynecologic Cancer Patients

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ABSTRACT

Objective: To study the correlation between creatinine clearances, calculated by Cockcroft & Gault equation and 24-hour urine collection in gynecological cancer patients treated with carboplatin.

Materials & Methods: Thirty-eight gynecological cancer patients who were treated with carboplatin at King Chulalongkorn Memorial Hospital from March 2008 to May 2009 were recruited. Creatinine clearances calculated by Cockcroft & Gault equation and 24-hour urine collection were compared. Data regarding age, height, lean body weight, and serum creatinine were also recorded.

Result: The mean age of the patients was 51.1 (SD = 8.4) years. The mean serum creatinine was 0.58 (SD = 0. 12) mg/dl. The mean creatinine clearance that was calculated by Cockcroft & Gault equation was 90.2 (SD=19.0) ml/min compared to 99.5 (SD = 21.8) ml/min estimated by 24-hour urine collection. Pearson correlation coefficient (r) between creatinine clearance calculated by Cockcroft & Gault equation and 24-hour urine collection was 0.61 (p < 0.01).

Conclusion: Moderate correlation between creatinine clearances calculated by Cockcroft & Gault equation and 24-hour urine collection in gynecological cancer patients was demonstrated.

Keywords: creatinine clearance, Cockcroft & Gault equation, 24-hour urine collection, serum creatinine

Introduction

Carboplatin is used as an adjuvant chemotherapy for almost all gynecologic cancer patients. Carboplatin[1-4] is known as renal eliminated drug, the dosage of which depends on assessment of renal function.

In practice, we usually used Calvert formula for calculated dose of carboplatin in which glomerular filtration rate (GFR) is one of the values that are used to determine the dosage.

Calvert formula = AUC (GFR + 25)

Regarding glomerular filtration rate (GFR) determination, there are many methods that are widely used. The generally accepted gold standard used

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for glomerular filtration rate (GFR) assessment is through the clearance of ^{99m}TC-DTPA[5-7]. However, this approach is cumbersome, difficult and time consuming, it is not practical for routine clinical use. 24-hour urine creatinine clearance[8], practically recommended for clinical use but the glomerular filtration rate (GFR), may be erroneous in poorly trained patients which can result in either inadequate or excess 24-hour urine volume. The most convenient way to determine glomerular filtration rate (GFR) is through calculation from one of the following equations such as Cockcroft-Gault[9], modification of diet in renal disease (MDRD)[10] and Jelliffe[11]. These equations are based on stable serum creatinine.

Cockcroft & Gault equation[9] is the most convenient and being widely available used to estimate glomerular filtration rate (GFR) in gynecological cancer patients. There are multiple variables that affect the creatinine clearance values such as age, body weight and serum creatinine. This equation is less reliable when calculated in patients with low level serum creatinine (defined as serum creatinine < 0.7 mg/dl)[12], who are usually found with epithelium ovarian cancer patients and commonly present with low body weight, low muscle mass as well as hypo-albuminemia.

At present, our institute uses Cockcroft & Gault equation to estimate creatinine clearance in patients treated with carboplatin[9]. In low level serum creatinine group the estimated by Cockcroft & Gault equation caused the error so we used the estimate from 24-hour collection of urine. In the practical, ideal estimates creatinine clearance method should be simple, convenient, fast and inexpensive.

The aim of this study was to evaluate the correlation between creatinine clearances that calculated by Cockcroft & Gault equation[9] and 24-hour urine collection in gynecological cancer patients. These correlation in subgroup of patients with low levels serum creatinine will also be evaluated.

Materials and methods

Gynecologic cancer patients who underwent surgery and had adjuvant treatment with 1st course of carboplatin at Department of Obstetrics and Gynecology King Chulalongkorn Memorial Hospital, Bangkok, Thailand from March 2008 to May 2009 were recruited in this study. They had no history underlying renal disease, never received any chemotherapy. Patients whose urine could not be completely collected, calculated by urine creatinine production rate (For Female : age < 50 years, urine creatinine = 15-20 mg/ lean body weight/day and age between 50-90 years, urine creatinine = [15-20 mg/ lean body weight/day]/2), who had unstable serum creatinine (whose serum creatinine levels is varied more than 0.3 mg/dl, punctured 2 times), had chronic kidney disease more than Stage III (creatinine clearance ≤ 60 ml/ min), all of them were excluded from the study. Informed consent was compulsory for recruitment. This study has received approval from the institutional review board (IRB) of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

Before the 1st post operative adjuvant carboplatin was started, medical records were reviewed to obtain demographic data and information on the presence of co-morbidities. Data regarding age, height and actual body weight were recorded, their lean body weight and body mass index (BMI) were calculated using these equation (Lean body weight for female = [0.65 x height in cm] - 50.74, BMI (kg/m^2) = weight (kg) / $height^2$(m)). Blood samples were drawn from all patients by venipuncture. All creatinine measurements were performed at the same laboratory by using Jaffe's method[13]. Creatinine clearance was estimated by Cockcroft & Gault equation (Creatinine Clearance = ([(140 – Age) x Lean body weight(kg) x 0.85]/ Serum Cr (mg/dl) (mL/min per 1.73 m^2)) and urine was collected over 24-hour period for estimated 24-hour urine creatinine clearance.

Statistical analysis:

The results were expressed as means. Statistical analysis of the study data was performed by Pearson product moment correlation coefficient to assess an association between continuous variables and assigned $P<0.01$ as statistical significant. We used SPSS software version 13.0 for Windows (SPSS Inc. Chicago, USA).

Results

All Gynecologic cancer patients who underwent surgery and had adjuvant treatment with 1st course of carboplatin at Department of Obstetrics and Gynecology King Chulalongkorn Memorial Hospital, Bangkok, Thailand from March 2008 to May 2009 were recruited in this study, 53 patients (except private case). 15 patients were excluded; 12 patients have chronic kidney disease more than stage III (creatinine clearance ≤ 60 ml/min) and 3 patients could not complete collection of the urine specimen. Therefore, 38 patients were enrolled into this study. The majority 35/38 (92%) patients in this study were epithelial ovarian cancer patients and the remaining were uterine cancer, Fallopian tube cancer and primary peritoneum cancer patients.

The characteristics of 38 patients are shown in Table 1. There are 30 patients in low level serum creatinine group (serum creatinine < 0.7 mg/dl)[10].

Table 1. Characteristics of the patients (n = 38)

Characteristics	Mean (SD)	Range
Age (year)	51.1 (8.3)	29 – 69
Height (cm)	153.6 (3.4)	146 – 160
Lean body weight (kg)	49.1 (2.2)	43.8 – 53.3
Actual body weight (kg)	57.1 (9.9)	39.4 - 83
BMI (kg/m^2)	24.4 (4.4)	16.2 – 34.2
Serum creatinine (mg/dl)	0.58 (0.12)	0.39 – 0.90

Table 2. Serum creatinine of the patients (n = 38)

Serum creatinine (mg/dl)	No. of patients (%)
0.90 – 0.99	2 (5.2)
0.80 – 0.89	1 (2.6)
0.70 – 0.79	5 (13.1)
0.60 – 0.69	7 (18.4)
0.50 – 0.59	14 (36.8)
0.40 – 0.49	8 (21)
0.30 – 0.39	1 (2.6)

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As shown in Table 3, Mean of creatinine clearance calculated by Cockcroft & Gault equation using lean body weight was 90.2 (SD = 19) ml/min. Mean of creatinine clearance calculated by Cockcroft & Gault equation using actual body weight was 105.5 (SD = 23.4) ml/min and mean of creatinine clearance by 24-hour urine collection was 99.5 (SD = 21.4) ml/min.

Table 3. Creatinine clearance calculated by Cockcroft & Gault equation and 24-hour urine collection (n = 38)

| Creatinine clearance	Mean (SD)	Range
CG lean body weight (ml/min)	90.2 (19)	60.7 – 134.2
CG actual body weight (ml/min)	105.5(23.4)	65.9 – 159.8
24-hour urine collection (ml/min)	99.5 (21.9)	63.0 – 156.3

CG – Cockcroft & Gault equation

As shown in Fig. 1-3, Pearson correlation coefficient between creatinine clearance calculated by Cockcroft & Gault equation using lean body weight and 24-hour urine collection was 0.61, p<0.01.
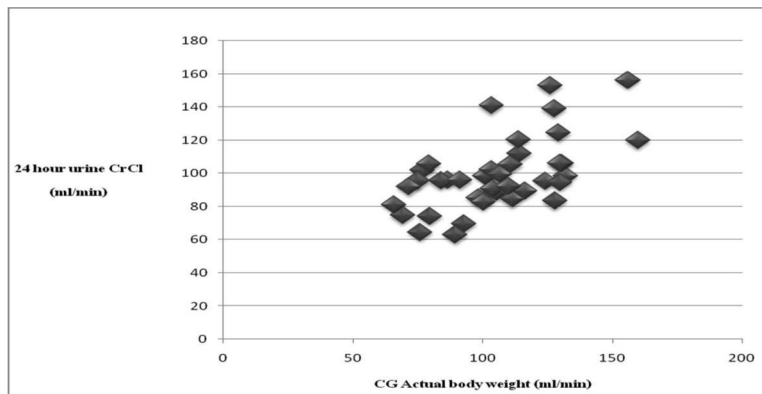
Pearson correlation coefficient (r) between creatinine clearance calculated by Cockcroft & Gault equation using actual body weight and 24-hour urine collection was 0.56 (p<0.01).
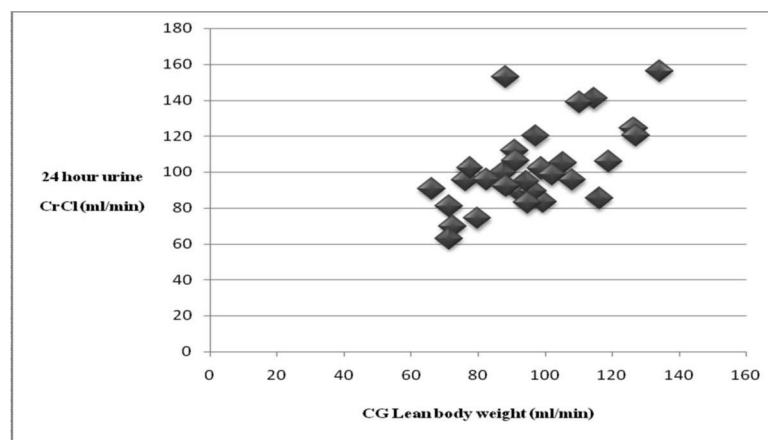
Pearson correlation coefficient (r) between creatinine clearance calculated by Cockcroft & Gault equation using lean body weight and 24-hour urine collection in patients with low level serum creatinine was 0.60, p<0.01.
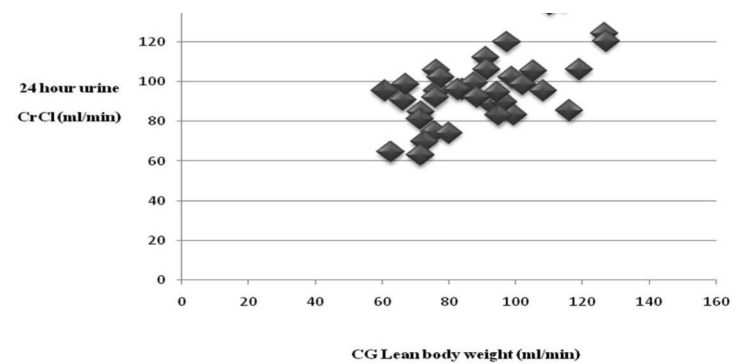
Fig 1. Correlation between creatinine clearance calculated by Cockcroft & Gault equation using lean body weight and 24-hour urine collection (n = 38)

Fig 2. Correlation between creatinine clearance calculated by the Cockcroft & Gault equation using actual body weight and 24-hour urine collection (n = 38)

Fig 3. Correlation between creatinine clearance calculated by the Cockcroft & Gault equation using lean body weight and urine 24-hour collection in low level serum creatinine group (n = 30)

Discussion

An accurate renal assessment for clinical use is essential especially for determining the dosage of cytotoxic drugs. Chemotherapy can cause nephrotoxicity, and renal impairment can result in altered excretion of chemotherapeutic agents, resulting in increased systemic toxicity.

Estimated glomerular filtration rate (GFR) through the clearance of [99m]TC-DTPA[5-7], the standard method, is very costly; invasive tests that require the administration of exogenous substances, catheterization and frequent blood draws are not practical for routine use. Estimated glomerular filtration rate (GFR) by determining creatinine clearance based on 24-hour urine collection and Cockcroft & Gault equation has show good correlation with[99m]TC-DTPA in a previous study.

Küng et al 1994[14] firstly reported comparison of kidney function in patients with ovarian cancer and treated with chemotherapy by Cockcroft & Gault equation and measurement of 24-hour urine creatinine clearance and regression analysis showed a moderate correlation between these two methods.

Fotopoulos et al 2006[15], compared six radionuclidic and non-radionuclidic methods for assessment of glomerular filtration rate (GFR) in patients with chronic renal failure. Correlation coefficient

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of creatinine clearance calculated by Tc^{99} DTPA and 24-hour urine collection was 0.91 and correlation of creatinine clearance calculated by Tc^{99} DTPA and Cockcroft & Gault equation was 0.79. They concluded that the radionuclidic methods in patients with chronic renal failure are reliable and reproducible, closely resembling those of inulin clearance. Among all radionuclidic methods, (99m) Tc-DTPA(+) showed the best correlation.

Barraclough et al 2009[16] studied in HIV-infected adults and reported correlation coefficient of 0.77 between creatinine clearance calculated by Cockcroft & Gault equation and Tc-99m Pentetate and correlation coefficient of 0.63 between creatinine clearance estimated urine 24-hour creatinine clearance and Tc-99m Pentetate.

Our study was different from other study, in which patients had advanced age, low body weight, low muscle mass and malnutrition so these patients usually have low level of serum creatinine, reveal moderate correlation between creatinine clearance calculated by Cockcroft & Gault equation and 24-hour urine collection which was similar to the study of Gerber et al 2006[17] who demonstrated in a group of primary CNS lymphoma patients treated with high-dose methotrexate. Their study shows Pearson correlation coefficient (r) = 0.49 (P < 0.0001) between creatinine clearance calculated by Cockcroft & Gault equation and 24-hour urine collection. The average MTX dose determined based on measured and calculated creatinine clearance were significantly correlated (r = 0.72, P < 0.0001).

Chronic kidney disease patients were excluded from our study. Accuracy of the estimated urine creatinine clearance is limited by the fact that as the glomerular filtration rate (GFR) falls, the rise in the SCr is partially opposed by enhanced creatinine secretion. Thus, in chronic kidney disease patients, creatinine excretion is much greater than the filtered load, resulting in a potentially large overestimation of the glomerular filtration rate (GFR).

Our study compared creatinine clearance calculated by Cockcroft & Gault equation and urine 24-hour cretinine clearance instead of other equation such as modification of diet in renal disease (MDRD) [10] and Jelliffe(11) because most of the pharmacokinetic studies with chemotherapeutic agents were performed using the Cockcroft-Gault equation.

The original article by Cockcroft DW, Gault MH 1976[9], creatinine clearance was calculated by lean body weight. While both lean and actual body weight were used in our study because in our daily practice we used actual body weight due to simplify and our study has demonstrated correlation between two method.

Our study reveals many advantages. The result shows correlation between creatinine clearance calculated by Cockcroft & Gault equation and 24-hour urine collection (r = 0.61, p <0.01). Mean dose of Carboplatin when creatinine clearance was calculated by Cockcroft & Gault equation using lean body weight was 575.9 mg compared to 622.5 mg using 24-hour urine creatinine clearance. Mean percentage error was 5.8% between these two methods, generally acceptable dose of carboplatin should not vary more than 20%.

Seventy nine percents (30/38) of the cases in this study had low-level of serum creatinine. Subgroup of low level serum creatinine patients had the same correlation (r = 0.60, p <0.01).

Nevertheless, our study did not compare creatinine clearance calculated by Cockcroft & Gault equation with standard method^{99m} TC-DTPA that is not practically used in our institute and we did not compare toxicity of patients between these two methods.

Further larger study are required to confirm this correlation and comparison of toxicity in patients after using these two methods should be analyzed to show clinical significance.

Conclusion

This study showed moderate correlation between creatinine clearance calculated by Cockcroft & Gault equation and 24-hour urine collection in gynecological cancer patients.

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การเปรียบเทียบค่า Creatinine Clearance จากการคำนวณตามสูตรของ Cockcroft & Gault และ จากการเก็บปัสสาวะ 24 ชั่วโมง ในผู้ป่วยมะเร็งทางนรีเวช

สมสุข สันติเบ็ญจกุล, นครินทร์ ศิริทรัพย์

วัตถุประสงค์ : ศึกษาความสัมพันธ์ระหว่างการประมาณค่า Creatinine Clearance จากการคำนวณตามสูตรของ Cockcroft & Gault และ จากการวัดโดยการเก็บปัสสาวะ 24 ชั่วโมง ในผู้ป่วยมะเร็งทางนรีเวช

วัสดุและวิธีการ : ศึกษาค่า Creatinine Clearance จากการคำนวณตามสูตรของ Cockcroft & Gault และจากการวัดโดยการเก็บปัสสาวะ 24 ชั่วโมง ในผู้ป่วยมะเร็งนรีเวช 38 คน ซึ่งวางแผนให้การรักษาด้วยยาเคมีบำบัด Carboplatin ณ โรงพยาบาลจุฬาลงกรณ์ ระหว่าง เดือน มีนาคม 2551 ถึง เดือน พฤษภาคม 2552

ผลการศึกษา : ค่าเฉลี่ยของระดับ Creatinine Clearance จากการคำนวณตามสูตรของ Cockcroft & Gault เท่ากับ 90.2 (SD=19.0) มล./นาที ค่าเฉลี่ยของระดับ Creatinine Clearance จากการวัดโดยการเก็บปัสสาวะ 24 ชั่วโมง เท่ากับ 99.5 (SD = 21.8) มล./นาที ค่า Pearson correlation coefficient (r) เท่ากับ 0.61 (p < 0.01) จากการคำนวณตามสูตรของ Cockcroft & Gault และ จากการวัดโดยการเก็บปัสสาวะ 24 ชั่วโมง การวิเคราะห์กลุ่มย่อย ในกลุ่มผู้ป่วยที่มีระดับ serum creatinine ต่ำ ค่า Pearson correlation coefficient (r) เท่ากับ 0.60 (p < 0.01)

สรุป : ค่า Creatinine Clearance จากการคำนวณโดยสูตรของ Cockcroft & Gault และจากการวัดโดยการเก็บปัสสาวะ 24 ชั่วโมง ในผู้ป่วยมะเร็งนรีเวช มีความสัมพันธ์กันในระดับปานกลาง