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The determination of renal function is a necessary component when individualizing dosage regimens for renally eliminated drugs. The calculated 24-hour creatinine clearance (CrCl) is probably the most valuable method for clinicians to assess renal function but is time consuming and inconvenient. Therefore, a number of equations have been developed to estimate CrCl. Many factors such as renal blood flow and CrCl may change post-conceptionally and continue to change throughout pregnancy. For this reason, dosing of medications that are renally eliminated in pregnant patients is often difficult.

The objective of this study was to:1) evaluate renal function during pregnancy using a measured 24-hour CrCl 2) to evaluate the performance of several published equations in predicting CrCl 3) to provide the clinician with an equation that best predicts the CrCl. One hundred forty-one pregnant women seen in Outpatient Obstetrics Clinic at Walter Reed were to be enrolled for study. As of September 1995, 112 patients in their first trimester were enrolled, however 46% of the patients were dropped because they failed to submit either the urine or blood samples. Additionally, the Obstetrics Department relocated to Bethesda Naval Hospital. Because of the strict time line and lack of personnel, the investigators were forced to terminate the project.

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Claudia B Mann 9-22-95

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INTRODUCTION

Nature of the problem

The determination of renal function is a necessary component when individualizing dosage regimens for renally eliminated drugs. The calculated 24-hour creatinine clearance (CrCl), derived by the serum and urinary creatinine, is probably the most valuable method for clinicians to assess glomerular filtration rate (GFR).[1] However, this method is often impractical because it is time consuming, expensive and inconvenient for both the clinician and patient. Therefore, a number of mathematical equations have been developed to estimate CrCl as a measure of renal function.

During the course of human gestation, many factors such as renal blood flow and CrCl are known to change post conceptionally and continue to change throughout the pregnancy.[2] In fact, renal blood flow may increase as much as 60% and GFR by as much as 50%.[3] Dosing of medications that are renally eliminated in pregnant patients is often difficult as the alteration in renal function can not always be accurately evaluated by the clinician. However, it is imperative that dosing be modified to reflect the change in elimination so as to avoid subtherapeutic or toxic levels.

An evaluation of several published CrCl equations on their ability to accurately predict renal function may provide data on their reliability in healthy pregnant women. Additionally, determination of an equation predictive of CrCl in pregnant patients may assist the clinician in more definitive dosing of drugs that are renally eliminated.

Objectives

A. To evaluate renal function using a measured 24-hour creatinine clearance in pregnant patients.

B. To evaluate the performance of several published equations in predicting creatinine clearance.

C. To provide the clinician with an equation that best predicts the creatinine clearance in pregnant patients so as to avoid empiric dosing of renally eliminated drugs.

Background

Most equations developed to predict renal function are based on the patients age, weight, gender and serum creatinine level. Creatinine is a byproduct of the breakdown of muscle metabolism. Since pregnancy is associated with an increase in body weight but not lean muscle mass, these predictions may either underestimate or overestimate renal function.

The derivation of the Cockcroft-Gault equation for prediction of creatinine clearance is based on serum creatinine, age and actual body weight. Their equation was derived from the regression line analysis of the mean 24-hour urinary creatinine excretion per kilogram of actual body weight and the mean age. A 15% correction factor was incorporated into the equation for women, as previous studies have shown that they have a lower fraction of muscle mass.[4]

Using the derived equation investigators attempted to predict creatinine clearances in 236 hospitalized patients. The calculated value was compared to the measured 24-hour urinary creatinine and a correlation coefficient of 0.83 was generated.[4]

The Lott-Hayton equation utilizes the same parameters as the Cockcroft-Gault equation. However, since creatinine is a byproduct of muscle metabolism it was thought that lean body weight should be substituted for actual body weight in the equation.[5]

Another study by O'Connell and colleagues enrolled 45 patients, aged 66 - 97, to evaluate the accuracy of eight equations used to estimate creatinine clearance.[6] The Jelliffe equation and the Cockcroft-Gault equation were the least biased and most precise as compared to a 24-hour measured CrCl. The investigators concluded that both the Jelliffe and the Cockcroft-Gault equations would be best to use in dosing drug therapy in elderly patients.

Luke and co-workers assessed five published equations for estimation of creatinine clearance in 109 subjects with varying degrees of stable renal function.[7] The equations of Mawer, Jelliffe 1, Jelliffe 2, which was based on age, Cockcroft-Gault and Hull were used to estimate the creatinine clearance. A 24-hour urine sample was obtained for measurement of creatinine excretion in all subjects. The subjects were instructed to remain in a reclining position for a four hour infusion of inulin. Both a urine

creatinine and measured inulin were obtained during this four hour reclining period. The predicted values were then compared to both measured inulin clearance as well as the creatinine clearance. The measured creatinine clearance in the patients correlated significantly with that of the four hour measurement of inulin ($r = 0.84$; $p<0.0001$) and creatinine ($r = 0.84$; $p < 0.0005$) clearance. The estimated creatinine clearance values predicted by Cockcroft-Gault and Mawer did not vary significantly from either the measured inulin or creatinine clearance. The linear regression for the Mawer ($r = 0.81$; $p < 0.0001$) and Cockcroft-Gault ($r = 0.81$; $p < 0.0001$) approximated that of the regression curve of the measured supine creatinine clearance. The authors concluded that the equations of Cockcroft-Gault and Mawer best predicted actual creatinine clearance values and should be employed for drug dosing.

Gral and Young evaluated the Siersbaek-Nielsen nomogram, Cockcroft-Gault, and Lott-Hayton equations for prediction of creatinine clearance in 26 patients, age 79 to 104.[8] The predictions were then compared to the measured 24-hour creatinine clearance using linear regression. The results showed statistically significant correlations in the three equations employed. The Lott-Hayton equation most significantly correlated with actual creatinine clearance ($r = 0.85$; $p < 0.00002$), followed by the Cockcroft-Gault ($r = 0.80$; $p < 0.00005$), and the Siersbaek-Nielsen nomogram ($r = 0.75$; $p < 0.0001$). It was concluded that these three methods are a satisfactory means of estimating creatinine clearance.

Another study conducted by Friedman and colleagues assessed the accuracy of the Cockcroft-Gault and Lott-Hayton equations in predicting creatinine clearance.[9] The study population consisted of 15 young (mean age = 24.8 years) and 15 elderly (mean age = 79.4 years) ambulatory individuals. Twenty-four hour urine collections were obtained from both groups and compared to the predicted creatinine clearance values as generated by the two equations. There was significant correlation with the Cockcroft-Gault equation ($r = 0.73$; $p < 0.005$) as well as with the Lott-Hayton method ($r = 0.60$; $p < 0.02$). However, the younger subjects had less significant correlation yielding a coefficient of 0.37 and 0.57 respectively. In addition, these equations frequently underestimated the creatinine clearance among the older female participants when compared to the actual measured 24-hour creatinine clearance. In conclusion, it was felt that both of these equations would provide sufficient means by

which clinicians could predict creatinine clearance in healthy elderly adults.

BODY

Plan

The original plan was for 140 women who are at least 18 years of age, currently within their first trimester of pregnancy, and seen in the Outpatient Obstetrics Clinic at Walter Reed Army Medical Center to be enrolled for study. Patients were excluded if they have disease states that may alter CrCl such as: chronic renal insufficiency defined as a serum creatinine > 2.0 mg/dL, diabetes, systemic lupus erythematosus, hepatic insufficiency defined as a total bilirubin > 2.5mg/dL or alanine or aspartate aminotransferase greater than twice normal,[10] hyperthyroidism, or toxemia of pregnancy. Patients were also excluded if they were taking medications that may effect CrCL such as: chronic glucocorticoids, trimethoprim, cotrimoxizole, or cimetidine.[11-13]

Once eligible for enrollment, the patients were followed for the entire gestation period and data to determine estimated and measured CrCl collected during each trimester.

By April of 1995, 55 patients were enrolled in the study. However, the dropout rate was much higher than originally anticipated. Dropout occurred when the patient failed to submit either a urine or a blood sample or the patient did not wish to participate after submitting their first set of samples (urine and blood). For this reason, an addendum was submittted to include all pregnant patients, regardless of trimester at the time of entry in the study. Up to 250 patients were to be enrolled and each would submit at least one urine and one serum sample sometime during their pregnancy. Assuming a minimal acceptable correlation coefficient for an equation is at least 0.75, a sample size of 250 was required for an estimated $r = 0.8$.

Measured CrCl. To obtain measured CrCl values, each subject was asked submit a blood sample at the time of their clinic visit for determination of serum creatitine. Each subject was also asked to collect a 24-hour urine sample within 7 days of their blood sample for determination of urine creatinine.

Serum creatinine concentrations was analyzed by an enzymatic method on Ektachem

Analyzer.[14] Urine samples were assayed for creatinine concentration using the Picric Acid Reaction on Nova Nucleus Analyzer.[15] The 24-hour urinary and serum creatinine values were used to calculate the measured creatinine clearance (Eq. 1) by the following equation:[16]

$$\textbf{Measured CrCl (mL/min)} = \frac{\text{(UCr[mg/dL])(urine volume[mL])}}{\text{(SCr[mg/dL])(time[min])}} \quad \text{(Eq. 1)}$$

where UCr is urine creatinine concentration and SCr is serum creatinine concentration.

CrCl Estimates. Estimated creatinine clearance will be determined using previously published mathematical equations: Cockcroft-Gault, Lott-Hayton, Jelliffe, Hull, Mawer, and Rowe. (appendix 1)[4,5,10,18,19] Estimates for each calculation will be computed using ideal body weight (IBW), and actual body weight (ABW), or body surface area (BSA). Height of each patient will be measured during the initial screening and weight determined at each clinic visit. Ideal body weight will be calculated from the following equation:[20]

$$\textbf{IBW = 45.5 + 2.3 kg/inch over 5 feet} \quad \text{(Eq. 2)}$$

Body surface area is calculated from the following equation:[21]

$$\textbf{BSA}(m^2) = 0.02350 \times \text{Ht } cm^{0.42246} \times \text{Wt } kg^{0.51456} \quad \text{(Eq.3)}$$

Equations to Estimate Creatinine Clearance

Cockcroft-Gault

$$CrCl = \frac{(140\text{-age}) \times wt}{72 \times SCr} \times 0.85$$

Jelliffe

$$CrCl = \frac{98 - 0.8(age - 20)}{SCr} \times \frac{BSA}{1.73} \times 0.9$$

Lott-Hayton

$$CrCl = \frac{(140\text{-age}) \times IBW}{72 \times SCr} \times 0.85$$

Hull

$$CrCl = \frac{(145 - age)}{SCr} - 3 \times \frac{(wt \times 0.85)}{70}$$

Mawer

$$CrCl = \frac{wt \times [25.3 - (0.175 \times age)] \times [1 - (0.03 \times SCr)]}{(14.4 \times SCr) \times (70/wt)}$$

Rowe

$$CrCl = (133 - 0.64 \times age) \times \frac{BSA}{1.73} \times 0.93$$

CrCl = creatinine clearance (mL/min)
wt = weight (kg)
SCr = serum creatinine (mg/dL)
Age in years
BSA = body surface area
IBW = ideal body weight (kg)

CONCLUSIONS

Summary of Funding

This study was recommended for funding by the Treservice Review Panel for the Defense Women's Health Research Program (DWHRP). Funds were managed by the Department of Clinical Investigation and the Directorate of Resources Management, WRAMC. The initial budget request for 140 patients and approximate amount used is listed below.

Initial Funding Request:

	FY 95	Approximate amount used as of 9/95
Laboratory Tests	$3,700	$3,000
Equipment/Supplies	$600	$484
Travel -	$2,000	0
Reprints -	$300	0
TOTAL	**$6,600**	**$3,484**

At the time the addendum was submitted, additional funding was requested for the increase in number of subjects. To encourage continued participation and increase recruitment, additional funding was also requested to reimburse subjects for each sample submitted. Funding was also requested to hire a temporary part-time nurse to assist in subject recruitment. Summary of request for additional funding is below, however it was never approved.

Summary of Additional Funding:

Laboratory tests/patient reimbursement	$12,500
Study Nurse	$20,000
Total	**$32,500**

Subject Recruitment

The initial sample size of 140 subjects was based on the submission of three sets of samples for each subject during each trimester. It was predicted that a sample size of 120 would provide 75% power to detect a standard deviation difference between predicted CrCl equations and the actual measured CrCl. Assuming a 15% attrition rate, 140 subjects were to be studied.

By April 1995, 55 subjects had been enrolled for study. However, the attrition rate was much higher than expected. Subjects were dropped from the study if they failed to submit either a urine or blood sample or the subject did not wish to participate after submitting both samples. For this reason, an addendum was submitted to include all subjects for study regardless of trimester. This was done because the study was to be completed by April 1996. However the sample size was increased to 250 subjects (approximately 83 subjects per trimester). This was based on the assumption that the relationship between the predicted and actual measure of creatinine clearance is not affected by the stage of the pregnancy.

By September 1995, 112 subjects were enrolled for study but the attrition rate was 48%. Of the 61 subjects that remained in the study, only 10 patients were in the second or third trimester. The remaining 51 patients were in their first trimester. Because subject recruitment and sample size was small, the objectives of the study were not met and conclusions could not be drawn.

Termination of Study

The current study was terminated for the following reasons:

1. The Obstetrics Clinic at Walter Reed relocated to Bethesda Naval Hospital during the summer of 1995. This would have required transferring the protocol to Bethesda, adding a collaborative investigator at that site, and getting IRB approval there to conduct the study. There was no knowledge of this relocation at the time the protocol was presented to the IRB for approval.

2. One of the primary investigators left her position at Walter Reed for personal reasons.

3. Strict time allotted for study, precluded adequate subject recruitment and/or transferring protocol to Bethesda Naval Hospital.

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