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Concordance between Drug Dosing Recommendations of Antimicrobials Based On Cockcroft-Gault and MDRD Equations In Patients With Chronic Renal Dysfunction

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Abstract:*The glomerular filtration rate (GFR) is the most precise measure of kidney function, however direct measurement of the GFR is difficult and expensive. With the introduction of the Modification of Diet in Renal Disease (MDRD) equation to calculate GFR in patients with chronic kidney disease, questions arise as to whether this method should be considered over the Cockcroft–Gault (CG) equation when making dosage adjustments for antimicrobials that are renally eliminated. The study was carried out to assess the concordance between drug dosing recommendations of antimicrobials based on Cockcroft-Gault and MDRD equations in patients with chronic renal dysfunction. Study populations of 75 patients were included as per the inclusion criteria. For each antibiotic, the match rate in dosing recommendation was compared with the hypothesized value of 85%. The match rate of amoxicillin/clavulanic acid and ofloxacin was found to be 100%, piperacillin/tazobactam 89.58%, levofloxacin 81.8%, vancomycin 66.6% meropenem 58.3%, and cefuroxime axetil 50%. When comparing doses derived from CG and MDRD equation, no statistically significant difference was seen for piperacillin/tazobactam (p = 0.1825),meropenem(p=0.1661),levofloxacin(P = 0.1669), vancomycin (p = 0.4226) and cefuroxime axetil (p = 0.5000). Overall the CG and MDRD equations rendered the same dose 83.3% of time (p = 0.9849). A positive correlation was found between CG and MDRD equations in the determination of renal function using CrCl and eGFR. However, there was a statistically significant difference existed between these two (p<0.05).*

Keywords:*Antimicrobialdrug dosing, Cockcroft-Gault equation, Modification of Diet in Renal Disease equation.*

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I. Introduction

Kidney diseases are global health problem[1]. According to the 2010 Global Burden of Disease Study, chronic kidney disease was ranked 27th in the list of causes of total number of global deaths in 1990, but rose to 18th in 2010[2]. In India 1 out of 10,000 are affected from chronic kidney disease and one lakh new diagnoses are with end stage renal disease annually. Literature reports thatdiabetes and hypertension are the commonest causes of CKD in India. Patients with stage III and stage IV have more severe reduction in GFR. These patients are at high risk for developing end stage of renal disease and death[3.]

The glomerular filtration rate (GFR) is the most precise measure of kidney function, but direct measurement of the GFR is difficult and expensive[4]. The 1998 Food and Drug Administration (FDA) guidance for industry recommends drug manufactures to employ the Cockcroft–Gault equation as a basis for drug-dosing. The Modification of Diet in Renal Disease (MDRD) equation was developed as an alternative approach for staging renal disease, and studies have confirmed the estimated GFR to be an accurate means of identifying chronic kidney disease[5].

Studies have compared the CG and MDRD equations for the dosing of medications and concluded that the differences in the doses rendered were too great to recommend use of MDRD for dosing.

Stevens et al. questioned the use of the CG equation for renal dosing and recommended that the MDRD equation replace the CG equation when determining renal dosing parameters in pharmacokinetic studies and adjusting medications in the clinical setting. The National Kidney Disease Education Program (NKDEP) subsequently recommended that the same renal estimate be used for dosing medications and staging CKD; NKDEP did not state a preference for MDRD or CG[6].

Dose individualization of drugs in patients with renal function impairment helps to achieve target drug concentration, thereby leading to optimize the therapeutic outcome[7].

Many drugs, including antimicrobials, are eliminated by renal excretion and require dosage adjustment in patients with renal dysfunction[8]. Recent studies comparing the CG and MDRD equations have highlighted a number of questions regarding the most appropriate equation to use when dosing medications that are cleared renally[4].

This information made us to perform a study to determine the concordance between the MDRD and Cockcroft-Gault equations in estimating GFR and the impact of using the MDRD equation versus the Cockcroft-Gault equation on antimicrobial dosing recommendations.

II. Objective

- The purpose of this study was to determine whether estimated creatinine clearance (CrCl) and estimated glomerular filtration rate (eGFR) can be used interchangeably when dosing common antimicrobials for patients with chronic kidney disease**.**

III. Materials And Methods

Study Design:
Prospective and retrospective data analysis
Study Duration:
10 months (from June 2017-March 2018)
Study Site:
General Medicine Department and Nephrology Department of a 750 bedded multispecialty tertiary care teaching hospital.
Inclusion Criteria:
Case records of patients of 20 years and above, with an eGFR less than 60mL/min/1.73m^2 and prescribed with at least one antimicrobial agent were included in the study
Exclusion Criteria:
Patients are excluded from the study if they are younger than 20 years, had an eGFR of 60 mL/minute/1.73m^2 or greater, end-stage renal disease with dialysis or had a documented diagnosis of acute renal failure.
Major Outcome Measure:
The primary outcome of this study is the frequency in which the estimated CrCl and eGFR rendered the same dose for the selected antimicrobials.

IV. Method:

The study was approved by the Institutional Ethical Committee (**SRH/EC.11-15/2017-18**). Eligible patients were identified through the patient's medical record review. Clinical and demographic details such as age, gender, weight, height, major diagnosis, co-morbid conditions, antibiotics and other medications prescribed, their strength and dosing schedule and relevant laboratory test results were recorded in customized data entry forms. A patient information form was prepared to inform the patient or the care givers about the purpose and necessity of the study. The patients were assured that the confidentiality will be strictly maintained. A patient consent form was prepared and written consent was obtained from the patient or from the care givers. The format contains details like address, date, place, provision for signature of the patient or caregivers, investigator and supervisor. Patients were included in the analysis if they are identified by physician diagnosis as having chronic kidney disease and are classified into either chronic kidney disease stage 3 (GFR 30–59 mL/min), 4 (15–29 mL/min), or 5 (<15 mL/min). Prospective review was carried out in the General Medicine Department and Nephrology Department while the retrospective analysis was carried out in the medical record department of the hospital. Both creatinine clearance and eGFR were estimated as follows:
Creatinine clearance was calculated by Cockcroft-Gault (CG) equation using the patient's Actual Body Weight (ACT) or Ideal Body Weight (IBW) as follows:

CG equation =[(140-age) × ACT×0.85 (if female)]/(72×SCr)

CGIBW equation = [(140-age) × IBW×0.85 (if female)]/(72× SCr)

For CG_{IBW}, IBW was calculated as 50 kg + [2.3 kg × (height in inches - 60)] for men and 45.5 kg + [2.3 kg ×(height in inches -60)] for women. If ACT (Actual body weight) was less than IBW, then ACT was used or if ACT exceeded IBW by >30%, ABW (Adjusted Body Weight) is used according to the following formula:

ABW =IBW + [(0.4 × (ACT-IBW)][9].

Estimation of GFR was performed by using the four variable MDRD (Modification of Diet in Renal Disease) formula:

eGFR =186.3 × (Serum creatinine)$^{-1.154}$ × (Age)$^{-0.203}$ × 1.212 (if black) ×0.742 (Female)[4].

The above parameters Creatinine clearance, eGFR and Ideal Body Weight (IBW) were calculated using Micromedex software. The dose suitable for each patient's estimated CrCl and eGFR were obtained from Micromedex database, package inserts, and published drug dosing guidelines and the resulting doses were then

compared. The frequency in which the equations provided the same dose is referred to as the "Match Rate." Concordance or discordance between dosing recommendations given by the two equations are expressed by "Match Rate".

This proposed study hypothesized that no significant difference exists in dosing recommendations between the CG and MDRD equations. For this hypothesis to be true, it was assumed that the dosing recommendations from each equation would match at least 85% of the time. For each drug, the match rate in dosing recommendations between the CG and MDRD equations was compared with the hypothesized value of 85% using a z-test for one proportion. Results were considered statistically significant if the observed level of significance was$P< 0.05$. All analysis was conducted using SPSS software (version 16.0).

V. Results And Discussion

Dosing concepts of 94 antibiotics were reviewed in 75 participants through retrospective and prospective analysis. Serum creatinine value of the patients ranged between 2 mg% - 5.4 mg% (2.89 ± 0.77). Demographic details of the study subjects are given in table no.1. Age and BMI of the study population were analyzed; details are given in table no.2 and 3. Patients were diagnosed to have chronic renal failure (100%), systemic hypertension (61%), diabetes mellitus (42.6%), anemia (16%), Ischemic Heart Disease (12%) and others.Stages of kidney disease, categorized into ESRD, severe and moderate renal impairment is depicted in table no.4

The total number of drugs prescribed in the study population was 550 and number of drugs prescribed per patient is shown in figure no.1. Their therapeutic categories are mentioned in table no.5. Antibiotics (17.09%), vitamins and minerals (16.54%), anti-ulcer drugs (10.18%) and anti-hypertensives (8.72%) were most frequently prescribed class of drugs. Piperacillin/tazobactam (51%), calcitriol (30.7%), clinidipine (46.8%) and pantoprazole (91.0%) was the most frequently prescribed medications.

Ninety four antibiotics of 12 different types were prescribed which included piperacillin/tazobactam(51.06%), cefuroxime axetil(2.12%), amoxicillin/clavulanic acid(5.31%), meropenem(12.76%), levofloxacin(11.7%), vancomycin(3.19%), ofloxacin(3.19%), ornidazole(3.19%) clindamycin (3.19%), metronidazole(1.07%) , ceftriaxone(2.12%) and linezolid(1.07%). Of these, 84 are renally cleared drugs (table no.6). Comparison of dosing of these antimicrobials by CG and MDRD equations were carried out. For each drug, the match rate in dosing recommendations was compared with the hypothesized value of 85%. The match rateof amoxicillin/clavulanic acid and ofloxacin was found to be 100%, piperacillin/tazobactam 89.58%, levofloxacin 81.8%, vancomycin 66.6%,meropenem 58.3%, and cefuroxime axetil 50%. When comparing doses derived from CG and MDRD equations, no statistically significant difference was seen for piperacillin/tazobactam ($p = 0.1825$), meropenem ($p =0.1661$), levofloxacin($P = 0.1669$), vancomycin ($p = 0.4226$), and cefuroxime axetil ($p = 0.5000$). There was no discordance observed for amoxicillin/clavulanic acid and ofloxacin.

Overall, the CG and MDRD equations rendered the same dose 83.3% of time ($p = 0.9849$) and Z value of -0.487 was obtained, indicating the hypothesis that no significant difference exists in dosing recommendations between the CG and MDRD equations is acceptable. A good correlation coefficient ($r =0.70$) was obtained showing the relationship between estimated GFR using theMDRD equation and CrCl using CG equation (figure no.2).

Table no 1 Demographic data (n=75)

S. No.	Characteristic	Values
1.	Mean age, yrs (range)	60.09 ± 12.35(26-85)
2.	Male %	61.3%
3.	Female %	38.6%
4.	Mean weight, kg, (range)	60.90 ± 8.50(45-86)
5.	Serum creatinine (mg/dL), mean, range	2.89 ± 0.77 (2 -5.4)
6.	Mean creatinine clearance mL/min, (range)	22.937 ± 7.1(10.2-43.1)
7.	eGFR(mL/min/1.73 m^2), mean,(range)	23.184 ± 7.529(8.4-43.1)
8.	Mean no. of drugs prescribed, (range)	7.33 ± 2.05(5-14)

Table no2: Age Categorization(n=75)

S. No.	Age group	Number	No%
1.	Early adulthood (19-35)	5	6.66
2.	Adulthood (36-50)	13	17.33
3.	Late adulthood (51-65)	24	32
4.	Young old (66-74)	28	37.33
5.	Old (75-84)	4	5.33
6.	Oldest old (>85yrs)	1	1.33

Table no 3: Body Mass Index(n=75)

S. No.	Category	Number	Percentage
1.	Under weight (<18.5)	2	2.66
2.	Normal weight (18.5 to 24.9)	56	74.6
3.	Over Weight (25 to 29.9)	16	21.3
4.	Obese class I (30 to 34.9)	1	1.3

Table no 4: Staging of kidney disease(n=75)

Staging of CKD based on CG equation.	No: of patients.	No %	Staging of CKD based on MDRD equation	No: of patients	No %
Moderate	12	16	Moderate	15	21.3
Serve	54	72	Severe	50	66.6
ESRD	9	12	ESRD	10	13.3

Table no5: Therapeutic category of drugs prescribed (n=31)

S. No.	Category	Total drugs	No%
1.	Vitamins and minerals	91	16.54
2.	Antibiotics	94	17.09
3.	Analgesics	16	2.90
4.	Diuretics	27	4.90
5.	Hypoglycemic agents	30	5.45
6.	Anti-hypertensive agents	48	8.72
7.	Hypolipidemic agents	17	3.09
8.	Anti-emetics	22	4
9.	Anti-hyperuricemic agents	20	3.63
10.	Anti-asthmatics	15	2.72
11.	Hormones	14	2.54
12.	Hepatoprotectants	10	1.81
13.	Anti-ulcerative agents	56	10.18
14.	Cardiac glycosides	3	0.54
15.	Antidote	5	0.90
16.	Phosphate binder	1	0.18
17.	Anti-anginal	8	1.45
18.	Immunosuppressants	3	0.54
19.	Laxative	1	0.18
20.	Anti-diarrhoeal	1	0.18
21.	Antacids	17	3.09
22.	Sedative –hypnotics	2	0.36
23.	Anti-parkinsonian	3	0.54
24.	Anti-arrhythmic agents	2	0.36
25.	Anti-tussives	5	0.90
26.	Cognition enhancers	1	0.18
27.	Anti –epileptic agents	12	2.18
28.	Anti-coagulants	6	1.09
29.	Anti-platelets	18	3.27
30.	Anti-histaminic	1	0.18
31.	Anti-cholinergic	1	0.18

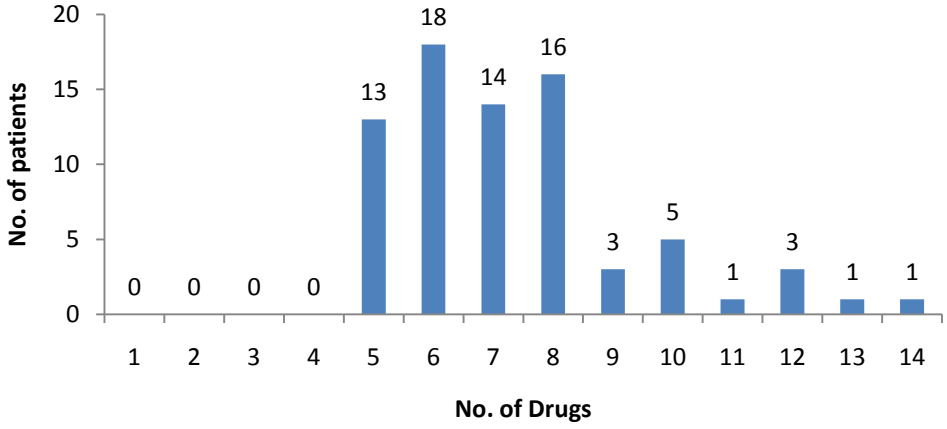

Fig no1: Number of Drugs prescribed per patient.

Table no 6: Antibiotics that are renally eliminated (n=84)

S. No.	Name of the drug	Number of patients	No %
1.	Piperacillin/tazobactam	48	57.14
2.	Meropenem	12	14.2
3.	Levofloxacin	11	13.09
4.	Amoxicillin-clavulanic acid	5	5.95
5.	Vancomycin	3	3.57
6.	Ofloxacin	3	3.57
7.	Cefuroxime axetil	2	2.38

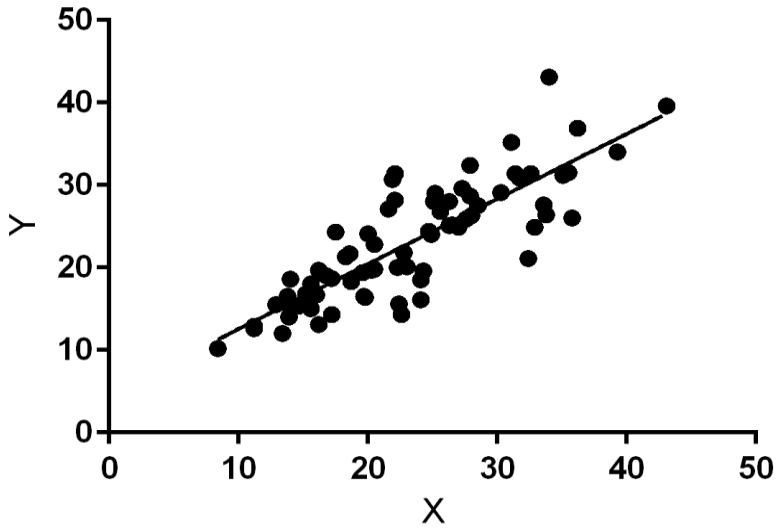

Fig no 2: Correlation between CG and MDRD equation

In the current study, CG-ABW equation was used for dosing calculation in 3 subjects as their ACT exceeded IBW > 30%. Whenever ACT exceeded IBW by > 30%, ABW was used [9].

Lessard and Kathyin their study hypothesized that no significant difference exists in dosing recommendations between CG and MDRD equations. Overall match rate using CG-IBW and MDRD equation was only 59.6% of time (p = 0.001) and there was no significant difference seen for metformin while comparing doses rendered by the two equations (P = 0.782)[6]. In the current study, the overall match rate was found to be 83.3% of time (p = 0.9849) and there was no statistically significant difference seen for dosing of piperacillin/tazobactam, (p = 0.1825), meropenem (p =0.1661), levofloxacin (P = 0.1669), vancomycin(p= 0.4226), and cefuroxime axetil

(p = 0.5000).

Dinsa et al 2017 compared CG, MDRD and CKD-EPI equations and the concordance between CG and MDRD equation was found to be 89.6% [10]. These findings are in agreement with the results obtained in the current study.

Golik and Kenneth reported that dosing discordance was observed for four antimicrobials 22.8% to 36.3% of times while comparing the doses by CG and MDRD equations. When doses were discordant MDRD equations provided higher dosing recommendations [11]. In the current study, discordance was observed in the dosing of five antimicrobials while comparing by CG and MDRD equations. These included piperacillin/tazobactam, levofloxacin, meropenem, vancomycin and cefuroxime axetil.

The match rate of piperacillin/tazobactam was found to be 89.58% and discordance occurs at eGFR< 20 mL/min/1.73 m^2 and 20-40 mL/min/1.73m^2. If the MDRD equation is used for the dosing, 80% of patients would require a reduced dose.

The match rate of levofloxacin, the fluoroquinolone antibiotic was found to be 81.8% and the discordance occurs at eGFR 20-49 mL/min/1.73 m^2 and the MDRD equation recommends higher dosing in all discordant cases.

Meropenem was prescribed for 12 patients and the match rate was found to be 58.3% and the discordance occurs at CrCl 10-25mL/min and 26-50 mL/min. CG equation recommends higher dosing.

The match rate of vancomycin and cefuroxime axetil was found to be 66.6% and 50% respectively. Discordance occurs at CrCl 50-20 mL/min and > 30 mL/min respectively and the CG equation recommends higher dosing.

Gill et al compared the four-variable MDRD and CG equations in the dosing of amantadine and digoxin in 180 long-term care facility patients and reported that if CG equation determined the dose of amantadine, 91.2% of patients would require a dose reduction[12].

In nutshell, MDRD equation recommends high dosing in 50% of discordant cases. The data analysis of current research indicated that there is a positive correlation between CG and MDRD equations in the determination of renal function using CrCl and eGFR values of the study subjects. However, there was a statistically significant difference existed between these two ($p<0.05$).

VI. Conclusion

Good concordance between CG and MDRD equations for antimicrobial drug dosing recommendation was obtained with "match rate" of 83.3%. However, evidence is insufficient to authenticate the interchangeability between the CG and MDRD equations when dosing of antimicrobials that are cleared renally. Currently in the drug information resources that specify a renal adjustment dosing method, the majority of doses are based on CG. Therefore, until the pharmaceutical manufacturers provide dosing recommendations based on eGFR in addition to CG-derived CrCl, CG should continue to be used for the dosing and the MDRD equations for the staging.

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