Title: Comparison of equations for dosing of medications in renal impairment

Short title: Renal function estimating equations

Original article

Authors: Aarati Khanal, Gregory M. Peterson, Matthew D. Jose, Ronald L. Castelino.

Aarati.Khanal@utas.edu.au

G.Peterson@utas.edu.au

Matthew.Jose@utas.edu.au

Ronald.Castelino@utas.edu.au

School of Medicine, University of Tasmania, Hobart, Tasmania Australia

Corresponding author:

Aarati Khanal, Unit for Medication Outcomes Research and Education (UMORE), School of Medicine, Division Pharmacy, Faculty of Health Science, University of Tasmania, Private Bag 26, Hobart, Tas. 7001, Australia.

Email: aarati.khanal@utas.edu.au

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Abstract

Aim: To determine the concordance among the Cockcroft-Gault, the Modification of Diet in Renal Disease (MDRD) and the CKD-Epidemiology Collaboration (CKD-EPI) equations in hypothetical dosing of renally cleared medications.

Methods: A total of 2163 patients prescribed at least one of the 31 renally cleared drugs under review were included in the study. Kidney function was estimated using the three equations. We compared actual prescribed dosages of the same drug to recommended dosages based on the kidney function as calculated by each of the equations and applying dosing recommendations in the Australian Medicines Handbook.

Results: There was a significant difference in the kidney function values estimated from the three equations ($P<0.001$). Despite the good overall agreement in renal drug dosing, we found selected but potentially important discrepancies among the doses rendered from the equations. The CKD-EPI equation non-normalised for body surface area had a greater rate of concordance with the Cockcroft-Gault equation than the MDRD equation for renal drug dosing.

Conclusions: There is need for a long-term multi-centre study in a diverse population to define the clinical effects of the discrepancies among the equations for drug dosing. Given the greater concordance of the non-normalised CKD-EPI equation with the Cockcroft-Gault equation for dosing, the recommendation by Kidney Health Australia and the United States National Kidney Disease Education Program that "dosing based on either eCrCl or an eGFR with body surface area normalisation removed are acceptable" seems suitable and practicable for the purpose of dosing of non-critical drugs in the primary care setting.

Key words: Kidney function, Kidney function estimating equations, MDRD equation, CKD-EPI equation, Cockcroft-Gault equation, eGFR

Introduction

Chronic kidney disease (CKD) is a significant and growing public health problem that is associated with premature mortality.[1] Renal impairment alters the effects of many drugs, sometimes decreasing their effects but more often increasing their effects and potentially toxicity.[2] Many of these changes are predictable and can be prevented by adjusting drug doses.[3] Traditionally, the creatinine clearance (CrCl) estimated by the Cockcroft-Gault equation[4] has been the most commonly used method to estimate renal function for drug dosing purposes, as evidenced by its widespread use in both drug developmental arenas and recommendations that appear in pharmaceutical product information.[4]

In recent years, several new equations have been proposed to estimate kidney function in patients with CKD; the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease – Epidemiology Collaboration (CKD-EPI) equations.[5,6] These latter equations, normalised for the patient's body surface area (BSA) and expressed in mL/min/1.73 m^2, are routinely used in Australian laboratories and health centres to automatically report eGFR with every request for serum creatinine determination.[7,8] There is abundant evidence that these two new equations provide more accurate estimation of the GFR;[9] however, there has also been discussion on whether these new equations could be used for renal drug dosing.[10-13]

Studies have questioned the use of the Cockcroft-Gault equation for renal dosing and recommended using MDRD for conducting renal pharmacokinetic studies and adjusting doses in the clinical settings.[14,15] The Cockcroft-Gault formula is prone to high variability due to inconsistent use of ideal, actual or adjusted body weight, and indicates the need for dosage adjustment more often due to a more conservative estimation of kidney function.[16,17]

The United States National Kidney Disease Education Program stated that either the Cockcroft-Gault or MDRD equation can be used as the estimate of kidney function for drug

dosing.[18] Similarly, in 2007 the Australasian Creatinine Consensus suggested that using the eGFR calculated with the MDRD formula was acceptable to assist with drug dosing decisions in general practice for non-critical-dose drugs.[19] This has led to considerable debate on the topic,[13,20] with some studies suggesting that Cockcroft-Gault should remain the equation of choice for drug dosing as the differences in the doses rendered were too significant to replace Cockcroft-Gault with MDRD for dosing.[13,21-25]

The CKD-EPI equation has been recommended to be used in clinical laboratories to routinely provide eGFR values with each request for serum creatinine.[26] There is, however, limited information on clinical application of this equation for the purpose of dose adjustment. Further, unlike MDRD, there has been no formal recommendation on use of this equation for drug dosing. However, it is worth noting that clinicians often use the eGFR provided by the laboratories for drug dosing purposes in the clinical setting.[27]

Given this background, we were interested to evaluate the agreement among the three formulae if hypothetically used in dosing of renally cleared drugs commonly prescribed in primary care settings. The two objectives of the study were (1) compare kidney function estimates based on the CKD-EPI, Cockcroft-Gault and MDRD equations, and 2) determine the concordance among the Cockcroft-Gault equation, MDRD (with and without BSA normalisation) and the CKD-EPI equation (with and without BSA normalisation) for hypothetical dosing of renally cleared medications.

Methods

We examined a sample of de-identified medication review cases extracted from the database of Medscope, an IT company providing decision support solutions for accredited pharmacists performing medication reviews. The Home Medicines Review and Residential Medication Management Review services were conducted by accredited pharmacists in collaboration

with GPs between January 2010 and June 2012. Methods for data extraction for this study have been explained previously.[28,29] Ethical approval was granted by the Tasmanian Health and Medical Human Research Ethics Committee.

All individuals (n=2163) who had their weight, height and serum creatinine reported and were prescribed one or more of the drugs under review, were included in the study. We used a list of 31 renally cleared drugs that are commonly prescribed in the community and recommended, by the Australian Department of Veterans' Affairs, to be avoided or used with dose adjustment in patients with renal impairment (Table 1).[30]

Kidney function was estimated using the MDRD, CKD-EPI and Cockcroft-Gault equations[4-6] and were analysed for any significant discrepancies (Supplementary Table 1). To further elucidate the impact of the observed discrepancies on drug dosing, for each patient we compared actual prescribed dosages of the same drug to recommended dosages based on the level of kidney function as calculated by each of the estimating equations and applying explicit recommendations for renal drug dosing in the Australian Medicines Handbook (AMH). For each drug, the prescribed doses were marked as 'appropriate (A)', 'inappropriate (IA)'', 'dose modification not required (NR)' ' based on the conformity with the adjustment specified in the AMH using the kidney function estimated from each equation. Both inappropriately high dose and contraindicated prescription were treated as inappropriate prescription Kappa coefficients along with pairwise percentage agreement were calculated to determine the concordance among the three equations.

The Cockcroft-Gault equation is reported unadjusted for body surface area in units of mL/min, whereas MDRD and CKD-EPI equations are adjusted for body surface area. The recommended unit for drug dosing recommended by the Kidney Health Australia is mL/min. Also, the Therapeutic Goods Administration (TGA) approved product information provides

dosing information by mL/min. Therefore, for the purpose of comparison, the GFR estimated using MDRD and CKD-EPI were converted to this unit, by multiplying each patient's BSA and dividing by 1.73 m^2 and the analyses were repeated.

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp., Excel 2010 (Microsoft Corporation, Redmond, USA) and ReCal online web service.[31] The analysis of variance (ANOVA) repeated measure test was used to determine the significance of differences in the kidney function estimates determined from the three equations (Cockcroft-Gault, MDRD and CKD-EPI). A P-value of less than 0.05 was considered as significant. The concordance in dosing recommendation for each drug based on the kidney function estimates from these equations was determined using Fleiss Kappa (K). Fleiss kappa is a statistical measure that calculates the reliability of agreement between more than two raters. It is a measure of the degree of agreement that can be expected above chance.[32]

Results

The clinical characteristics of study participants are summarised in Table 2. The mean age of the patients was 72.2 years and 59.5% were female. The ANOVA repeated measure test demonstrated a statistically significant difference in the kidney function values rendered from the three equations (P<0.001). All pairwise comparisons between the values for eGFR and eCrCl were significantly different from each other (P<0.001).

Table 3 shows the concordance among the three equations in dosing of the renally cleared drugs. The level of agreement ranged from moderate to very good. Concordance among the equations was lower for drugs that have fewer kidney function categories for dose adjustment.

When the analyses were repeated for the CKD-EPI and MDRD study equations with the removal of BSA normalisation (expressed in units of mL/min), a higher concordance was observed among the three equations (Table 3). Both the CKD-EPI and MDRD with the removal of BSA normalisation showed greater concordance to the Cockcroft-Gault equation than the normalised equations. Table 4 shows the pair-wise comparison of the MDRD and the CKD-EPI equations with the standard Cockcroft-Gault. In comparison to the MDRD equation, the CKD-EPI equation had a greater concordance with the Cockcroft-Gault equation for renal drug dosing. This pattern was consistent with all the drugs tested.

At an individual level the discordance in the doses rendered from the equations was considerable. For each drug the number of patients who required dosage adjustment or were prescribed doses higher than the recommended dose differed depending upon the equation used to estimate renal function (Table 3). For instance, 39.5% and 38.8% of the patients receiving metformin would require dose adjustment if Cockcroft-Gault and CKD-EPI equations were used, respectively, to estimate the kidney function. However, 52.4% of the patients would require dosage adjustment based on the MDRD equation.

Discussion

We found a statistically significant difference in the kidney function estimations rendered from the three equations in the same group of patients. The overall differences in the mean eGFR values were quite small; however, at an individual level they gave estimates that differed substantially. We cannot determine which equation best approximated the true

kidney function in our study due to lack of actual measures of kidney function. Further, the validation of the equations was not the purpose of this study.

We found a good agreement between the eGFR and eCrCl for dosing of non-critical drugs. Our results suggest that the equations have moderate-substantial agreement in dosing of non-critical drugs in primary care settings. This finding is consistent with the study by Steven *et al*, which concluded that there was little difference in the drug dose that would be administered using eCrCl and eGFR.[33] The normalisation of eGFR had an impact on drug dosing decisions; there was a higher level of agreement among the equations when the normalisation to BSA was removed from the eGFR values. This aligns with the National Kidney Disease Education Program's (NKDEP) suggested approach that either an eCrCl or an eGFR with BSA normalisation removed are acceptable for drug dosing estimations.[34]

We found that the CKD-EPI equation, not adjusted for BSA, had the highest concordance with the Cockcroft-Gault equation for both estimating renal function and the dosing of the renally cleared drugs. This finding is consistent with the previous literature which demonstrated that the CKD-EPI equation non-normalised to the BSA correlated more closely with the Cockcroft-Gault equation than did other formulae.[35] Similarly, in another study, the non-normalised CKD-EPI equation (mL/min) was found superior to the normalised CKD-EPI equation in estimating GFR (mL/min/1.73 m^2) for drug dosing.[36] Using the GFR (mL/min) as the reference for dosing, the CKD-EPI with the removal of BSA normalisation (mL/min) was associated with greater dosing concordance of carboplatin.[36] The non-normalised CKD-EPI (mL/min) provided results which were less biased and comparable at predicting GFR (mL/min) at higher levels of GFR and body mass index.[37,38]

A possible explanation for these findings would be that in this and the previously mentioned studies, the mean BSA for the sample was about 2 m^2.[38] The BSA of 1.73 m^2 is the average

normal mean value for young adults. The main purpose of reporting eGFR normalised to BSA was to allow harmonisation of results in individuals of various body size.[39] The normalisation or removal of it will have little effect for patients whose BSA is close to 1.73 m^2. However, for elderly people, or in patients whose body size is very different than average, the BSA should be considered.

The Cockcroft-Gault equation has been used as the preferred method to assess kidney function for drug dosing in the past. With the introduction of new classification of CKD, the new MDRD equation was used for diagnosing and staging CKD. This equation was later suggested for drug dosing. However, more recently, it has been suggested that the CKD-EPI is the most accurate method for estimating GFR.[6,40] Compared with the MDRD study equation, it provides less negative bias at values higher than 60 mL/min/1.73m^2 and more accurate estimation of eGFR in diverse populations.[41] Use of a single kidney function estimate for detection, drug dosing and management of CKD would facilitate better health care delivery in the primary care setting.[42] With laboratories automatically reporting CKD-EPI eGFR estimates, this equation, if validated for drug dosing, would be a useful tool for health professionals and potentially address the confusion associated with the existing practice of using different formulae for different purposes.

The performance of renal estimating equations in renal dosing have been evaluated in various instances and discrepancies have been reported. However, very little is known on the clinical outcomes of the observed discrepancies.[43] The differences in dosing based on different estimates of creatinine clearance may, in many cases, be clinically unimportant, or can be further refined based on clinical response. There is a need for a long-term multi-centre study in diverse populations to define the clinical effects of such discrepancies. In the interim, for individuals in whom the three equations provide substantially different estimates of kidney function or when prescribing drugs with narrow therapeutic indices or dose-dependent

toxicities, assessing kidney function using alternative methods such as measured CrCl or measured GFR using exogenous filtration markers should be considered. It is also recommended that prescribers use the available estimates along with their best judgement and clinical response to determine renal dosing for individual patients.[44,45]

Limitations

It should be noted that most of the discrepancies in drug dosing between equations might occur near the boundary between levels of renal function. These cut-offs could be arbitrary and not very precise with regards to drug clearance. In some cases, doses can double depending on which side of the boundary the renal function estimation falls. Moreover, it is accepted that clinical decisions may often over-ride the renal dose recommendations.

Laboratories provide serum creatinine measurements based on the creatinine assays that are aligned to the reference isotope-dilution mass spectrometry (IDMS) in Australia.[19] The MDRD Study equation has been re-expressed for standardised serum creatinine.[46] The CKD-EPI equation was developed using creatinine assays that are IDMS-aligned. However, the Cockcroft-Gault equation has not been re-expressed for use with standardised serum creatinine.[47] This might have contributed to the observed discrepancies among the equations.

The MDRD equation has been found to have a negative bias at values higher than 60 mL/min/1.73m^2.[48] This equation tends to overestimate eGFR values in patients above 60 mL/min/1.73 m^2, indicating need for dose adjustment less frequently.[49] Some of the drugs examined in the study, such as metformin, gabapentin and pregabalin, have dose adjustments recommended near or above 60 mL/min.

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Table 1. Prescribing recommendations for renally cleared medications examined in the study[a]

Drugs/Usual maximum dose	Dosage adjustment in relation to CrCl values	
	Creatinine Clearance, mL/min	**Maximum dosing recommendation, mg**
Metformin 500-3000 mg daily	60–90	2000 daily
	30-60	1000 daily
	<30	Avoid use
Glibenclamide 2.5–20 mg daily	≤50	Avoid use
Saxagliptin 5 mg once daily	<50	2.5 once daily
Sitagliptin 100 mg once daily	30–50	50 once daily
	<30	25 once daily
Vildagliptin 50 mg twice daily	<50	50 once daily
Perindopril *Perindopril arginine*, 5 -10 mg once daily *Perindopril erbumine,* 4-8 mg once daily	30–60	2.5/2 mg once daily
	15–30	2.5/2 mg alternate days
	<15	2.5/2 mg on day of dialysis
Olmesartan 20 -40 mg once daily	<30	Avoid use
Valsartan 80-320 mg once daily	<30	80 once daily
Fenofibrate 145 mg once daily	20–60	96 once daily
	10–20	48 once daily
	<10	Avoid use
Zoledronic acid[b] 5 mg once per year	<30	Avoid use
Alendronate 10 mg once daily *or* 70 mg once a week.	< 35	Avoid use
Ibandronic acid *Oral* 50 mg once daily *IV* 6 mg every 4 weeks	30–50	Oral: 50 every second day, IV: 4 every 4 weeks
	<30	Oral:50 once each week, IV:2 every 4 weeks
	<10	Avoid use
Risedronate 5 mg once daily or 35 mg once a week or 150 mg once a month	<30	Avoid use
Clodronate 1600-3200 mg daily	50–80	1600 daily
	30–50	1200 daily
	10–30	800 daily
	<10	Avoid use
Tiludronate 400 mg once daily	<30	Avoid use
Strontium 2000 mg once daily	<30	Avoid use
Teriparatide 20 micrograms once daily	<30	Avoid use
Duloxetine 30-120 mg once daily	<30	30 once daily
Bupropion 150-300 mg once daily	≤ 50	150 once daily
Rivaroxaban 15 mg twice daily for 3 weeks, then 20 mg once daily.	<15	Avoid use
Dabigatran 150 mg twice daily	30-50	110 twice daily
	<30	Avoid use
Pregabalin 75-300 mg twice daily	30–60	300 in 1 or 2 doses
	15–30	150 in 1 or 2 doses.
	<15	75 as single dose.
Gabapentin 300-3600 mg daily	50–79	600–1800 daily in 3 doses
	30–49	300–900 daily in 2/3 doses.

	15–29	600 daily in 2/3 doses.
	<15	300 daily
Levetiracetam 250-1500 mg twice daily	50–79	500–1000 twice daily
	30–49	250–750 twice daily
	<30	250-500 twice daily
Memantine 5-20 mg daily.	5–29	10 once daily
Paliperidone 3–12 mg once daily	50–80	6 once daily
	30–50	3 once daily/Avoid injection
	10-30	3 once daily
	<10	Avoid use
Pramipexole 125 micrograms-1500 mg 3 times daily	20–50	2.25 once daily
	<20	1.5 once daily
Varenicline 0.5-2 mg once daily	<30	1 daily
Solifenacin 5-10 mg once daily	<30	5 once daily
Tolterodine 1-2 mg twice daily	<30	1 twice daily

[a]All recommendations are based on the Australian Medicines Handbook [b]Indication for osteoporosis

Table 2. Patients' Characteristics

Characteristics	Mean (SD) or %
Age, years	72.2 (11) Range, 26:99
≥65	84.3
Female	59.5
Weight (kg)	80.7 (20.9)
Height (cm)	163.6 (10.2)
SrCr (µmol/L)	91.2 (40.3)
BMI, kg/m^2	30 (7)
>30 kg/m2	45.1
BSA, m^2	1.9 (0.27)
Cockcroft-Gault (mL/min)	73.5 (38.9)
MDRD eGFR (mL/min/1.73 m^2)	71.8 (25.4)
CKD-EPI eGFR (mL/min/1.73 m^2)	66.2 (21.2)

Note: values expressed as mean (standard deviation) Abbreviations: BSA- body surface area, BMI-body mass index CG, Cockcroft-gault equation using actual body weight; MDRD, Modification of Diet in Renal Disease Study equation; CKD-EPI Chronic Kidney Disease – Epidemiology Collaboration

Table 3. Concordance in renal drug dosing among the renal function estimating equations[#]

Drug/Dosing Level	N received this dose	Cockcroft-Gault (mL/min)			MDRD (mL/min/1.73 m^2)			MDRD* (mL/min)			CKD-EPI (mL/min/1.73 m^2)			CKD-EPI* (mL/min)			Overall agreement (Fleiss Kappa)	
		NR	IA	A	NR	IA	A	NR	IA	A	NR	IA	A	NR	IA	A	CG vs MDRD vs CKD-EPI	CG vs MDRD* vs CKD-EPI*
Dosing Level (1)																		
Alendronate	253	219	34	-	244	9	-	242	11	-	238	15	-	236	17	-	0.51	0.60
Risedronate	201	186	15	-	199	2	-	195	6	-	194	7	-	192	9	-	0.33	0.62
Strontium	69	61	8	-	67	2	-	66	3	-	67	2	-	66	3	-	0.46	0.61
Duloxetine	74	68	4	2	71	2	1	72	2	-	70	3	1	70	3	1	0.75	0.62
Dosing Level (2)																		
Sitagliptin	126	94	22	10	103	14	9	105	12	9	100	16	10	102	14	10	0.71	0.82
Dabigatran	48	35	-	13	40	1	7	42	-	6	38	1	9	40	1	7	0.51	0.57
Dosing level (3)																		

Perindopril	620	296	240	84	376	185	59	411	157	52	331	218	71	374	179	67	0.69	0.73
Fenofibrate	150	96	33	21	85	43	22	101	31	18	78	49	23	96	33	21	0.74	0.77
Metformin	956	377	133	446	232	173	551	402	113	441	335	198	423	371	128	457	0.58	0.68
Pregabalin	68	31	4	33	36	2	30	45	1	22	33	3	32	41	1	26	0.21	0.64
Dosing Level (4)																		
Gabapentin	63	18	7	38	15	4	44	26	2	35	14	2	47	22	5	36	0.54	0.57
A-appropriate dose, IA- inappropriate dose that is defined as inappropriately high dose and contraindicated prescriptions, NR-dose modification not required																		

*not normalised to body surface area

[#]Dosing level refers to the number of kidney function categories for dose adjustment as specified in AMH.

The last column shows the Fleiss Kappa value which indicates the level of concordance among the three equations CG, MDRD, CKD-EPI (both normalised for BSA and non-normalised for BSA) in dosing of the renally cleared drugs.

Table 4. Concordance in drug dosing recommendations using the Cockcroft-Gault Versus Unadjusted MDRD and CKD-EPI for specific drugs

Drug	**Kappa value** **Average Pairwise Percent Agreement (%)**	
	MDRD* (mL/min)	**CKD-EPI* (mL/min)**
Alendronate	0.46 90.1	0.60 92.0
Risedronate	0.52 95.0	0.61 95.5
Sitagliptin	0.73 90.4	0.81 92.8
Dabigatran	0.50 83.3	0.55 85.4
Perindopril	0.63 79.1	0.71 83.8
Fenofibrate	0.69 84.6	0.90 95.3
Metformin	0.57 73.9	0.70 84.6
Pregabalin	0.55 75.0	0.85 92.6
Gabapentin	0.63 79.6	0.70 85.9

Abbreviation: MDRD, Modification of Diet in Renal Disease Study equation; CKD-EPI Chronic Kidney Disease – Epidemiology Collaboration

*not normalised to body surface area