Use of the Cockcroft-Gault versus the MDRD Study Equation to Dose Medications: An Opinion of the Nephrology Practice and Research Network of the American College of Clinical Pharmacy

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Abstract

Accurate assessment of kidney function is an important component of determining appropriate medication dosing regimens. Nearly all manufacturer-recommended dose adjustments are based on creatinine clearance ranges derived from clinical pharmacokinetic studies performed during the drug development process. The Cockcroft-Gault (C-G) equation provides an estimate of creatinine clearance and is the equation most commonly used to determine drug doses in patients with impaired kidney function. Recently, the Modification of Diet in Renal Disease Study (MDRD) equation has also been proposed for this purpose. Published studies report that drug doses determined by the two equations do not agree in 10-40% of cases. However, interpretation and comparison of these studies is complicated by the variable creatinine methods used for calculating C-G and MDRD estimates, the patient populations studied, and a lack of outcomes data demonstrating the clinical significance of dosing discrepancies. Moreover, the impact of reporting standardized serum creatinine values on the accuracy of the C-G equation and corresponding drug dosing regimens have been questioned. Currently, no prospective pharmacokinetic studies have been conducted using the MDRD equation to generate dosing recommendations, and limited data are available to support its use in some patient populations representing demographic extremes. Collectively, these issues have resulted in considerable confusion among clinicians and have fueled a healthy debate on whether or not to use the MDRD equation to dose medications. Each of these issues is reviewed, and a proposed algorithm for using creatinine-based kidney function assessments in medication dosing is provided. Knowledge of the advantages, limitations, and clinical role of each equation will facilitate their safe and effective use in medication dosing.

Introduction

The goal of dose individualization in patients with impaired kidney function is to maximize the likelihood that target drug concentrations will be achieved and thereby lead to an optimal therapeutic outcome. Calculation of estimated creatinine clearance (CL_{CR}) via the Cockcroft-Gault (C-G) equation (Figure 1)[1-4] has been the most commonly used method to estimate kidney function for drug dosing purposes for decades. This approach stems partly from prospective pharmacokinetic (PK) studies often conducted during drug development that are designed to establish the relationship between drug elimination and kidney function (usually CL_{CR}), per the 1998 U.S. Food and Drug Administration (FDA) Guidance pertaining to PK studies in patients with impaired kidney function.[5] In recent years, several new equations have been proposed to estimate kidney function in patients with chronic kidney disease (CKD).[6-8] In 2009, the National Kidney Disease Education Program (NKDEP), an initiative of the National Institutes of Health (NIH), updated its recommendations regarding drug prescribing to state that either C-G or the Modification of Diet in Renal Disease Study (MDRD) equation (Figure 1) can be used as the estimate of kidney function for drug dosing.[4] Also, the FDA has recently proposed that the MDRD equation be incorporated, in addition to C-G, into future PK studies in patients with kidney disease, and that PK results be shown for both estimates of kidney function.[9,10] Others have suggested that C-G should remain the equation of choice for drug dosing, which has led to considerable debate on the topic.[11-15]

There are many important factors to consider when assessing studies comparing the performance of C-G and MDRD for drug dosing. These factors include the weight used in the C-G equation, the adjustment for body surface area in the MDRD equation, the use of a standardized serum creatinine concentration, and the methods used in the original PK studies

from which dose recommendations for the medications being studied were derived. The current lack of prospective PK data and dosing recommendations generated using the MDRD equation creates further challenges. In addition, the limitations and the study population of the original trials from which the estimating equations were developed must be considered before applying either equation to a specific patient.

In response to the continued controversy surrounding use of the MDRD equation to dose medications in patients with impaired kidney function, the American College of Clinical Pharmacy (ACCP) Nephrology Practice and Research Network (PRN) presents the strengths and limitations of using each method to dose medications. In addition, the implications of creatinine standardization are reviewed, and limitations of applying the C-G and MDRD equations to select populations are outlined. Lastly, an algorithm is proposed for using creatinine-based kidney function assessments in drug dosing.

Creatinine-Based Indices of Kidney Function

Both the C-G and MDRD equations utilize a serum creatinine concentration along with other patient characteristics to provide an estimate of kidney function. Assessment of kidney function by any equation that employs serum creatinine concentrations has inherent limitations. Patient characteristics that influence creatinine generation (i.e., severe liver disease, and conditions associated with altered muscle mass, including cachexia and malnutrition) or disposition, such as unstable kidney function, may render creatinine-based equations inaccurate. In addition, creatinine is both filtered at the glomerulus and undergoes active tubular secretion, a process that contributes a disproportionately greater percentage to renal clearance as the glomerular filtration rate (GFR) declines.[16] Thus, CL_{CR} tends to overestimate true GFR,

particularly at lower levels of kidney function, because of the additional creatinine cleared by tubular secretion.

The C-G equation provides an estimate of CL_{CR}. It was derived from 24-hour creatinine clearance measurements from 249 men who had an average measured CL_{CR} of 73 mL/min.[1] In their equation, Cockcroft and Gault reported using total body weight, but recommended using ideal or lean body weight in patients with pronounced obesity or volume overload. Because no women were included in the study, the adjustment for female sex (15% reduction in CL_{CR}) in the C-G equation was based on earlier recommendations to reduce CL_{CR} by 10-20% in women.[1] Despite these limitations, the C-G equation has performed well compared to direct measures of CL_{CR}. Moreover, it has been used by researchers and clinicians to estimate CL_{CR} in patients with stable kidney function for over three decades, in accordance with FDA-approved drug dosing recommendations to individualize dosing in patients with impaired kidney function.

The MDRD equation provides an estimated GFR (eGFR). It was developed using data collected from 1,628 patients with an average measured GFR (determined via ^{125}I-iothalmate clearance) of 40 mL/min/1.73 m^2.[6] The 4-variable form of the MDRD equation is currently the most widely used and provides an eGFR that is normalized for body surface area (BSA) in units of mL/min/1.73 m^2. Use of the MDRD equation is not recommended in those with a GFR > 60 mL/min/1.73 m^2 because of decreased accuracy.[7] When used for drug dosing, it has been recommended that the MDRD eGFR value be individualized ($MDRD_{IND}$), i.e., not normalized for BSA and converted to units of mL/min (Figure 1), particularly in patients whose BSA is considerably larger or smaller than 1.73 m^2.[4]

Currently, little information has been published on the performance of the MDRD equation in the elderly (age > 65 years), obese, individuals with liver disease, and races other

than Caucasian or African-American, and the findings have been inconsistent.[14,17-21] This may be due partly to different ranges of GFR in the populations studied, a variety of serum creatinine assay methods, and inconsistent procedures used for measuring GFR. Modified versions of estimating equations have been developed for specific subgroups, including diabetic (modified C-G) and Japanese patients (modified MDRD), but have not been widely tested in the clinical setting.[22,23] Newer versions of eGFR equations, such as the CKD-EPI equation, have been proposed but are yet to be fully adopted into clinical practice.[8]

Serum Creatinine Standardization

Serum creatinine is the key variable used in both the C-G and MDRD equations. There are numerous assays and instruments used by clinical laboratories worldwide to measure serum creatinine concentrations, and substantial differences exist between many. For example, some assays measure non-creatinine chromogens in addition to serum creatinine. Historically, serum creatinine assays were not standardized, which further contributed to significant interlaboratory variability in reported values. In 2003, Miller and colleagues evaluated bias in serum creatinine concentration results based on fresh-frozen serum samples from 5,624 U.S. laboratories participating in the College of American Pathologists (CAP) Chemistry Survey and representing 50 instrument-assay combinations; mean bias ranged from -0.06 to +0.31 mg/dL (Figure 2).[24] The median bias of the instrument–assay peer groups compared to true creatinine values was +0.12 mg/dL.[24] Assays used were alkaline picric acid (kinetic, rate-blanked kinetic or end point methods) and enzymatic methods. The influence of non-creatinine chromogens and calibration bias on serum creatinine concentration results are particularly influential on estimates of kidney function when GFR is higher (i.e., the proportional influence of bias is greater at higher GFRs;

Figure 3). In addition, MDRD eGFR has a negative bias and more variability versus measured GFR at higher GFR values, which can result in under-prediction of GFR and false diagnosis of kidney disease in individuals with normal kidney function.[25] Consequently, the NKDEP recommends reporting a specific number for the eGFR value only when eGFR < 60 mL/min/1.73 m^2, and to report "≥60 mL/min/1.73 m^2" for higher values.[25]

In an effort to reduce interlaboratory variability in serum creatinine concentration reporting and to improve subsequent reliability of eGFR results worldwide, the NKDEP Laboratory Working Group in collaboration with the International Federation of Clinical Chemistry and Laboratory Medicine and the European Communities Confederation of Clinical Chemistry created the Creatinine Standardization Program.[25] These groups have been working with clinical laboratories and assay manufacturers to calibrate all serum creatinine assays to be traceable to an isotope dilution mass spectrometry (IDMS) reference measurement procedure.[26] An assessment of major manufacturers in 2009 indicated that nearly all had completed recalibration of creatinine methods to be traceable to an IDMS reference method.[27] Currently, all creatinine assay methods from major manufacturers in the U.S. have calibration that is either traceable to or very comparable to an IDMS reference method. It was predicted that all laboratory stocks of non-IDMS traceable reagents and calibrators were exhausted by the end of 2010.[28] Essentially all U.S. clinical laboratories are now reporting standardized serum creatinine values, which facilitates use of a common equation for estimating GFR and consistent interpretation to more accurately identify individuals with kidney disease. Importantly, the original 4-variable MDRD Study equation was re-expressed for use with IDMS standardized serum creatinine values (Figure 1).[3] Specifically, the original constant 186 was reduced by 5.9% to 175 to account for the differences between original non-standardized MDRD Study serum

creatinine concentrations and standardized creatinine concentrations resulting from differences in the slopes of the corresponding regression lines.[3] This re-expressed equation should now be used in place of the original 4-variable MDRD equation.[8]

The blood samples from the original Cockcroft and Gault study are no longer available, so it is not possible to re-express the C-G equation using standardized creatinine concentrations as has been done with the MDRD equation. The Cockcroft and Gault study utilized a serum creatinine assay procedure that separated creatinine from many interfering substances (non-creatinine chromogens) commonly found in serum. The next generation of serum creatinine assays measured creatinine directly in serum and were affected by non-creatinine chromogens causing the results to be higher than those used to develop the C-G equation. However, there was no modification of the C-G equation (or other estimating equations that were based on serum creatinine concentrations) to compensate for higher results. From the 1990s until the creatinine standardization program was complete in 2010, routine serum creatinine laboratory methods had a variable, but predominantly positive bias (-6 to +31% in 2003 CAP survey) relative to an IDMS reference measurement procedure (Figure 3) and there was no quantitative relationship between any of these contemporary assay methods and the assay method used to develop the C-G equation.[24,28,29]

When standardized serum creatinine values are used today to estimate CL_{CR} with the C-G equation, estimated CL_{CR} values will be systematically higher (typically about 5-10%) than those observed prior to implementation of standardized creatinine assays. The effect of creatinine standardization on C-G derived CL_{CR} calculations using the median bias of 0.12 mg/dL reported in the 2003 CAP survey[24] is presented in Figure 4 (example 1). Since the estimated CL_{CR} is slightly higher on average after the standardization, some corresponding drug dosages may also

be higher in a given patient than during the pre-standardization time period. This is problematic given that dosage adjustment guidelines for many drugs were developed prior to creatinine standardization.

It is not clear at this time what the overall impact might be, but using the C-G equation (or any CL_{CR} or GFR estimating equation developed before standardized serum creatinine reporting) with standardized serum creatinine concentrations may result in higher corresponding drug doses, on average, than in the pre-standardized creatinine era. Some have suggested adding the median bias of 0.12 mg/dL to reported standardized creatinine values when using the C-G equation.[24] We believe this practice should be discouraged due to the large variability in the mean bias from various assay/instrument combinations reported (Figure 3).[24] Similarly, others have proposed multiplying the C-G value by a variable adjustment factor of 0.8 to 0.95.[7,13] The full impact of these approaches on dose calculations and subsequent patient outcomes requires further evaluation before either can be advocated.

Some institutions have developed regression equations to show the relationship between IDMS standardized serum creatinine concentrations and serum creatinine concentrations generated prior to recalibration (i.e., using non-IDMS standardized 'legacy' standards).[30] This is particularly useful in clinical or research settings where longitudinal serum creatinine values are being compared prior to and after serum creatinine recalibration. But, it is unlikely that most laboratories will conduct a statistically valid comparison using large numbers of samples from individuals representing the full spectrum of kidney function. Unfortunately, conflicting information regarding creatinine standardization is being disseminated. Some websites are promoting use of a single regression formula to "back-calculate" standardized creatinine values to non-standardized values in order to use the C-G equation.[31,32] This is similar to adding the

median bias of 0.12 mg/dL from the 2003 CAP survey to the standardized creatinine value, which as mentioned previously, we do not recommend. A more recent CAP Comprehensive Chemistry Survey from 2010 included 40 different assay reagent/instrument combinations from eight different manufacturers for measurement of creatinine in serum or plasma.[28] Given the large number of assay reagent/instrument combinations in use today, no one single formula can be applied or single number can be added to estimated serum creatinine values that will give results similar to non-standardized serum creatinine values recorded at individual institutions prior to creatinine standardization.

Currently, only one pediatric and two adult GFR estimating equations have been developed for use with standardized serum creatinine values; the re-expressed MDRD and CKD-EPI equations,[7,8] and the Schwartz equation for children.[33] Despite the fact that the majority of institutions are using a standardized creatinine method, clinicians still need to know the specific assay used in their institution. Standardization of serum creatinine assays only addresses the calibration of the assay for a "typical" sample and does not address the influence of non-creatinine chromogens or other interfering substances (e.g., drugs, hemoglobin) that may be present in a particular serum sample and that may alter values with specific assays.

Use of the C-G Equation for Drug Dosing

Creatinine clearance is a composite index of kidney function, including glomerular filtration and tubular secretion, which are both important contributors to renal (and total) drug clearance. The relationship between CL_{CR} and total drug clearance has been confirmed for hundreds of drugs and new molecular entities during clinical development over the past three decades. The historical and current approach to adjusting drug dosing regimens in patients with

impaired kidney function is based on pharmacokinetic studies conducted in patients whose level of kidney function is usually determined by measured or estimated CL_{CR}.[34] This pharmacokinetic data is the source for dose adjustment algorithms that appear in FDA-approved drug labels, as well as secondary and tertiary references.[34]

Clinicians utilize a variety of approaches to estimate CL_{CR} in the clinical setting, based largely on their judgment of what is the most appropriate method for the clinical characteristics of the patient. In a survey of 204 members of the ACCP Nephrology and Critical Care PRNs conducted in 2009, over 95% of practitioners reported using the C-G equation to estimate CL_{CR} for dose adjustments in patients with CKD.[35] None of the survey respondents reported using the MDRD equation for renal dosing.[35] A review of prescribing information for 250 drugs approved by the FDA from 1998-2007 showed that dose adjustment recommendations based on CL_{CR} were provided for 44 compounds, with the C-G equation being specifically recommended in 11 (25%), and use of either actual or ideal body weight in the C-G equation specified in 5 (11%).[35]

The findings of several retrospective studies suggest that, although results of the MDRD and C-G equations are both highly correlated with measured GFR, use of the MDRD equation often overestimates CL_{CR} leading to errors in drug dosing when compared to doses calculated using C-G.[36-39] For example, in 409 patients with stages 3-5 CKD, use of the MDRD equation resulted in kidney function estimates that were 14-28% higher ($p<0.001$) than C-G derived CL_{CR} estimates, leading to discordant dose adjustments in 20-36% of patients for eight antibiotics including cefazolin, cefepime and meropenem.[36] This could translate into patients receiving higher drug doses using MDRD derived eGFR compared to C-G derived estimated CL_{CR}. Others have reported similar findings in which median $MDRD_{IND}$ values overestimated CL_{CR} by nearly 40% in 207 hospitalized patients with stable kidney function.[39] This resulted in dose calculations

that were higher than C-G based recommendations for cefepime in 54% and 57% of patients with CL_{CR} values in the range of 11-30 mL/min and 31-60 mL/min, respectively. Similar discordance rates were also reported for levofloxacin, meropenem, and piperacillin/tazobactam. Although the clinical significance of administering larger doses of drugs that have a wide therapeutic range is not known, there is a potential for larger doses to lead to higher drug costs and adverse drug events, especially in high-risk populations such as the elderly.

Dosing discrepancies with the use of C-G and MDRD equations have also been reported for drugs with a narrow therapeutic range, such as amantadine, dofetilide, digoxin, gentamicin, epifabitide and enoxaparin.[15,40,41] In the largest retrospective study to date (46,942 patients) comparing use of the C-G and MDRD equations for drug dosing, the MDRD eGFR identified about 50% fewer patients for dose adjustment of glycoprotein IIb/IIIa inhibitors (epifabitide and tirofiban) and the low-molecular weight heparin enoxaparin as the C-G equation.[40] Major bleeding events were more frequent for individuals who received an excess dose of glycoprotein IIb/IIIa inhibitors as assessed by MDRD compared to C-G (21.8% vs 17.8%, respectively). The odds ratios for major bleeding with excess doses based on MDRD or C-G were 1.57 (95% CI: 1.35-1.84) and 1.31 (95% CI: 1.12-1.54), respectively. Major bleeding events were similar among patients receiving enoxaparin.[40] Substitution of the MDRD equation in place of C-G could also have significant implications with the antiarrhythmic agent dofetilide, which is known to have dose-related alterations in the QTc interval and has explicit dosing instructions in the prescribing information based on the C-G equation.[42-44]

Altogether, the results of several retrospective studies suggest that use of the MDRD equation for drug dosing purposes often yields higher doses than the C-G equation, which many believe is a safety concern. To date, available evidence does not support the superiority of the

MDRD equation over C-G for drug dosing, or the universal substitution of C-G with the MDRD equation for drug dosing purposes. C-G typically yields a more conservative estimate and indicates the need for dose adjustment more often.[15,40,41] Therefore, until safety concerns are adequately addressed in prospective studies evaluating the relationship between MDRD eGFR and drug exposure and response, the most conservative kidney function estimate should be used with narrow therapeutic window drugs and high-risk subgroups such as the elderly (Figure 5).

Use of the MDRD Study Equation for Drug Dosing

The MDRD equation has been shown to provide more accurate estimates of GFR than C-G.[45] As such, MDRD derived eGFR has become the standard metric for detection, evaluation, and monitoring of CKD in the clinical and public health arenas. Currently, at least 80% of U.S. clinical laboratories automatically report eGFR along with serum creatinine concentrations.[46] The widespread availability of an automatically reported eGFR value affords pharmacists a tool that, if validated for drug dosing, could easily be incorporated into clinical pharmacy practice for this purpose. Also, automatic calculation of eGFR may render it more reliable than CL_{CR}, which is prone to high variability due to clinicians' inconsistent use of body weight (e.g., actual, ideal, lean or adjusted) and rounding low serum creatinine concentrations up to 1 mg/dL or other number during manual calculations.[47] Moreover, use of a single kidney function estimate for management of kidney disease and drug dosing, and harmonization of practice in this regard between pharmacists and other clinicians would be ideal.

Recent studies have assessed the utility of MDRD derived eGFR for drug dosing and suggest that it may be used in lieu of C-G derived estimated CL_{CR}. A retrospective comparison of MDRD derived eGFR, C-G using actual weight, and C-G using ideal body weight ($C\text{-}G_{IBW}$)

with measured GFR (^{125}I-iothalamate clearance) was recently conducted in a pooled data set of 5,504 patients.[48] Estimated GFR and CL_{CR} were used to assign patients to kidney function categories established by the FDA for renal drug dosing adjustment, and the level of concordance between them was determined. In addition, dosage recommendations for 15 commonly used medications that are cleared by the kidneys were simulated using each of the kidney function measures and the level of concordance between them was also assessed. Standardized creatinine values were used in all equations. Kidney function was expressed for all three calculations in mL/min. The $MDRD_{IND}$ equation demonstrated greater concordance with measured GFR (78%) than C-G (73%) or C-G_{IBW} (66%) for assignment to FDA renal drug dose adjustment categories. C-G and C-G_{IBW} results were in agreement with the $MDRD_{IND}$ -based assignment to FDA drug dose adjustment categories in 78% and 75% of cases, respectively. The concordance rates between the kidney function estimates and measured GFR for drug dosing recommendations was best for $MDRD_{IND}$ (88%) compared to C-G (85%) and C-G_{IBW} (82%). Of the three estimating methods, the C-G equation was most likely to generate higher recommended drug dosages, and C-G_{IBW} was most likely to generate lower recommended drug dosages. The study findings with the most important implications to clinical pharmacy practice pertain to the agreement observed between the $MDRD_{IND}$ equation and C-G (89%) and C-G_{IBW} (88%) for recommended drug doses. The $MDRD_{IND}$ equation generated dosing recommendations that were lower than C-G in 9% of the study population and higher in 10% when the C-G_{IBW} was used.[48] Overall, these concordance rates are in agreement with previous studies,[37,39] and suggest that, in most cases, use of the $MDRD_{IND}$ equation for drug dosing purposes will generate similar recommendations to C-G and C-G_{IBW}.

Recent studies also suggest that the MDRD equation is a safe alternative to C-G for dosing highly toxic anticancer drugs. A retrospective comparison of carboplatin doses calculated using MDRD derived eGFR or C-G estimated CL_{CR} versus measured GFR (^{99m}Tc-DTPA) was performed in a data set of 96 patients with gynecological malignancies.[49] The study showed that the MDRD equation was more accurate than the C-G, with better precision and similar bias to C-G compared to measured GFR, and led to carboplatin doses within 3% of the C-G derived dose.[49] That said, carboplatin doses were calculated using the Calvert Formula, which was originally derived from GFR measured by ^{51}Cr-EDTA clearance, so a high correlation between MDRD and measured GFR-derived doses would be expected. A similar comparison of carboplatin doses based on the MDRD equation and C-G in 36 patients demonstrated good correlation (r = 0.88) between the equations, and correcting the MDRD result for body surface area ($MDRD_{IND}$) improved the correlation (r = 0.94).[50] Lastly, the doses of ten anticancer drugs excreted by the kidneys (non-carboplatin) generated using the MDRD equation were compared to doses based on C-G in a recent retrospective analysis of 313 oncology patients.[51] The doses derived from the two equations were concordant in 286/313 (91%) of patients. In the 27 discordant cases, 18/27 (67%) of patients would have received a higher dose using the MDRD equation. The authors noted that the MDRD eGFR values were not individualized since the correlation between GFR and BSA is questionable in cancer patients. The importance of kidney function evaluation for chemotherapeutic dosing, the confusion surrounding it, and the urgency of clarifying the optimal approach was recently corroborated in an open letter from the NIH National Cancer Institute to physicians performing clinical trials or treating patients with carboplatin.[52] Collectively, these data suggest that the MDRD equation may be a reasonable alternative to the C-G for chemotherapeutic dosing, but further evaluation of GFR estimation in

cancer patients, including use of individualized values, is warranted to confirm the findings above.

Numerous published studies focus on the discordance between drug doses derived from the MDRD equation and C-G, commonly reporting rates between 10%-40%, and speculate on the potential dangers of such differences (i.e., adverse patient outcomes).[14,36-39] Interestingly, these differences are comparable in magnitude to those generated using different versions of the C-G equation (i.e., using actual, 'adjusted', or ideal body weight),[47,53] and those introduced by inappropriately rounding serum creatinine concentrations.[54,55] Yet, by using sound clinical judgment in the selection and dosing of drugs, particularly in our most vulnerable patients such as the elderly, the use of different versions of C-G safely continues today. Moreover, although it is not ideal, this practice continues despite a lack of recommendations pertaining to specific forms of C-G in FDA-approved drug labels.

Limitations of the C-G and MDRD Equations in Select Populations

Use of the C-G and MDRD equations requires stable kidney function and steady-state serum creatinine concentrations. The equations should be used cautiously, if at all, in patients with fluctuating serum creatinine concentrations such as the critically ill, individuals with acute kidney injury, and patients requiring renal replacement therapy. Clinicians who practice in a setting where clinical information systems automatically report a C-G CL_{CR} and/or MDRD eGFR must recognize that these systems may not identify patients with these conditions. It is necessary to evaluate patients for the presence of these conditions prior to applying either of these equations. Furthermore, application of the C-G and MDRD equations in two unique

populations that often require medication dosing adjustments warrant specific consideration: the elderly and the obese.

Elderly

Interpretation of serum creatinine values within the context of reduced muscle mass is an important consideration in older adults. Clinicians are often presented with frail elderly patients with serum creatinine concentrations of less than 1.0 mg/dL. Some clinicians suggest rounding the concentration up to 1.0 mg/dL; however, this is an approach that is not supported by evidence. Golik and colleagues found that the C-G estimate using serum creatinine concentrations rounded up to 1.0 mg/dL correlated best with the MDRD estimate in patients older than 60 years, but this study did not have a measured GFR reference.[39] Rounding the serum creatinine concentration to 1.0 mg/dL has also led to underestimation of estimated CL_{CR}.[54]

Also of note are the differences in the derivation of the C-G and MDRD equations in that the decline in kidney function with age is expressed linearly with the C-G equation and exponentially with the MDRD equation. This point was recently illustrated by plotting estimates determined for a 70-kg man as serum creatinine and age varied.[13] For the individual with a serum creatinine concentration of 1.5 mg/dL, the estimated CL_{CR} decreases linearly for C-G, but the eGFR declines in a curvilinear fashion for MDRD. The MDRD estimate of kidney function becomes substantially higher at age 60 and above, and the differences are most pronounced in patients with lower serum creatinine concentrations.[13] This should be considered when evaluating kidney function in older individuals. It is when such discrepancies in estimates exist that other methods, such as a measured CL_{CR}, may be warranted to more accurately evaluate the patient's kidney function (Figure 5).

There is limited information on the performance of the MDRD equation in the elderly. The MDRD Study population consisted of patients aged 18-70 years.[6] Stevens and colleagues did evaluate the performance of the MDRD equation re-expressed for use with a standardized serum creatinine concentration in subgroups of a large pooled dataset (n=5504), including patients 65 years and older (n=580).[17] For those over 65 years old, the MDRD equation was less influenced in individuals with a GFR < 60 mL/min/1.73 m^2, but tended to overestimate measured GFR at the higher levels of kidney function.[17] In contrast, others have reported that both the C-G and MDRD equations underestimated measured GFR (determined by inulin clearance) in elderly patients (n=61) in an acute care setting.[18] The accuracy and precision of both methods were further diminished in patients with higher levels of kidney function (GFR > 90 mL/min/1.73 m^2) and in patients with diabetes mellitus.[18] While there are differences in these studies, one consistent finding is that the MDRD equation is less accurate at higher values of GFR in the elderly, consistent with findings in the overall population. Therefore, when using the MDRD equation in older individuals, it should be limited to use in those with decreased GFR (i.e., < 60 mL/min/1.73 m^2).

Discrepancies between C-G and MDRD derived drug dosing regimens have been observed in elderly patients. In a recent study that used gentamicin clearance as a marker of kidney function, the $MDRD_{IND}$ value overestimated gentamicin clearance by 29%, with differences of up to 69% in patients over 80 years of age.[19] In comparison, the C-G equation underestimated gentamicin clearance by 10%.[19] An evaluation of drug dosing recommendations in 180 elderly patients in a long-term care facility revealed that mean MDRD values were 40% higher than BSA normalized C-G derived estimates (72.9 mL/min/1.73 m^2 versus 52.1 mL/min/1.73 m^2, respectively).[14] Using the MDRD estimate, amantadine dose recommendations

would have been >35% higher than with the C-G, and 32% of patients would have received higher initial doses of digoxin with MDRD versus C-G estimates of kidney function. A limitation of these studies is that they are based on dose recommendations rather than pharmacokinetic outcomes.

A clinical example serves to illustrate differences in estimates of kidney function that might be observed in clinical practice and the importance of using sound judgment during their evaluation. Estimates of kidney function for a hypothetical elderly patient using the MDRD, $MDRD_{IND}$, $C\text{-}G_{IBW}$, and $C\text{-}G_{TBW}$ are displayed in Figure 4 (example 2). The MDRD estimates are higher than those determined by either C-G method, so clinically, the C-G equations may suggest that a dosage decrease is indicated while the MDRD results would not. If the serum creatinine is rounded to 1.0 mg/dL, then a dosage decrease would most certainly be required with the C-G equation. The practice of rounding up serum creatinine concentrations in an effort to improve estimates of kidney function, although common, is not evidence-based. The examples in Figure 4 are provided to highlight the clinical implications of adopting this approach.

Obesity

While obesity *per se* does not influence creatinine metabolism or muscle mass, it may lead to increased renal plasma flow and GFR.[56] There is a lack of consistency and agreement regarding approaches to estimate kidney function in the obese patient population, due partly to an underrepresentation of obese or overweight subjects in clinical trials.[57] The original MDRD study did not include morbidly obese individuals; the mean weight in the MDRD study population was 80 kg.[6] The MDRD investigators later evaluated the performance of the re-expressed MDRD equation in a more diverse population.[3,17] This population included overweight

(BMI 26-30 kg/m^2, n=999) and obese (BMI > 30 kg/m^2, n=1039) individuals.[17] The MDRD tended to underestimate measured GFR in those with measured GFR > 60 mL/min/1.73 m^2. The precision of the MDRD equation, indicating the percent of eGFR values within 30% of measured GFR, was also lower (82%) for obese individuals compared to that reported in the original MDRD study population (90%).[6,7,17]

Comparisons of the MDRD and C-G_{TBW} equations and measured GFR (^{99m}Tc-DTPA) in both obese and lean subjects with normal kidney function suggest that the MDRD equation underestimates GFR at every level of body mass index.[20] The C-G_{TBW} resulted in underestimation of GFR in non-obese individuals (-13 mL/min/1.73 m^2) and overestimation in the obese (+10 mL/min/1.73 m^2). Incorporation of the lean body weight (LBW) as derived by Duffull and colleagues into the C-G equation provides less biased estimates of kidney function in hospitalized morbidly obese (mean BMI of 50 kg/m^2) patients than use of total body weight or adjusted body weight when compared to measured 24-hour CL_{CR}.[21,58]

Clinicians must be aware of the implications of using different body size descriptors (i.e., ideal body weight versus lean or adjusted body weight, or individualization of the MDRD equation based on patient specific BSA) in estimating equations. In addition, clinicians must be aware of the body size descriptors utilized in automatically reported C-G or MDRD estimates at their institutions. As seen in Figure 4, example 3, obesity may lead to discrepancies in kidney function estimates and corresponding dosing regimens, particularly with the C-G_{TBW} equation. Specific instructions are provided in the package insert of some drugs to use either actual body weight (daptomycin, dofetilide) or ideal body weight (adefovir, tenofovir) in the C-G equation. Some publications have alternatively proposed using an adjusted body weight (i.e., 40% of difference between IBW and actual body weight) or the Salazar-Corcoran equation to estimate

CL_{CR} in obese patients.[47,59] The use of adjusted body weight has been validated for dosing of aminoglycosides,[60,61] yet this practice is often applied to other agents prescribed in overweight and obese individuals. Approaches involving direct measurement of LBW in those with extreme or morbid obesity have also been proposed.[21] In fact, use of LBW in the C-G equation for individuals with a total body weight of 99 kg to 320 kg resulted in estimates that were much closer to measured CL_{CR} compared with eGFR using the MDRD equation.[21] Although a CL_{CR} or GFR estimating method remains to be validated in patients with obesity, LBW appears to be the best body size descriptor to use when estimating CL_{CR} via C-G in this population.[62]

Future Directions: Role of the FDA

The 1998 FDA guidance on pharmacokinetic studies in patients with impaired kidney function recommended use of renal dose adjustment categories derived from CL_{CR}.[5] This was based partly on the rationale that CL_{CR} was 'widely used in patient care settings as a measure of renal function', and thus 'more practical than most other alternatives as a criterion for adjusting dosage in outpatient and inpatient settings'.[5] However, since publication of the 1998 FDA guidance, the MDRD derived eGFR was developed and is now widely reported in patient care settings,[46] no longer rendering CL_{CR} estimates more practical (based on widespread availability alone) than other alternatives for dose adjustment.

Currently, the FDA is considering including the MDRD Study equation in a revised version of the 1998 FDA guidance, which was presented at the FDA Advisory Committee for Pharmaceutical Sciences and Clinical Pharmacology in March 2010.[9,63] This draft proposal includes dosing tables based on the MDRD eGFR and C-G equations, and it was debated extensively.[63] Some expressed concerns that inclusion of an MDRD-based dosing table in the

package insert would be confusing for many practitioners because the unit of measure of the MDRD, mL/min/1.73 m^2, is not consistent with the C-G units of mL/min, and that the need to convert the MDRD eGFR to an individualized value in mL/min may be overlooked in the clinical setting. Going forward, drug dosing recommendations based on eGFR equations, in addition to C-G CL_{CR}, may be included in FDA approved drug dosing labels. If validated in prospective pharmacokinetic studies, this may facilitate the progression of clinical practice to using a single kidney function estimate for management of kidney disease and drug dosing. For drugs already approved by the FDA with existing renal dose adjustment recommendations based on CL_{CR}, manufacturers will likely not provide additional eGFR-based dosing recommendations.

Recommendations

A fundamentally important aspect of providing pharmaceutical care, which may also serve to minimize the clinical significance of the discordance between the MDRD equation and C-G based drug dosing regimens, deserves attention. That is, use of sound clinical judgment and critical thinking skills, including a review of the primary pharmacokinetic literature, during the assessment of all clinical information when considering drug selection and dosing, rather than rendering decisions solely on an estimate of kidney function.[64] Neither FDA-approved drug labels, common drug information sources, nor the NKDEP recommendations are references for how to dose specific drugs in all patients.[65] Differences between equations for estimating kidney function and drug dosing will always exist. Therefore, regardless of the equation used, clinical judgment must prevail.[37] A proposed algorithm for assessing kidney function and determining corresponding drug dosing regimens is presented in Figure 5. When presented with different kidney function estimates that potentially translate into different drug dosing regimens, clinicians

must choose the regimen that optimizes the risk-benefit ratio given the patient-specific clinical scenario. For drugs with a narrow therapeutic range, typically more conservative renal function estimates and corresponding doses should be used,[15,40,41] particularly if therapeutic drug monitoring is not readily available. In contrast, a more aggressive dosing strategy may be acceptable for drugs with a wide therapeutic range and a broader margin of safety, particularly when the potential implications of therapeutic failure may justify larger doses. Alternatively, clinicians may decide to use agents that are not predominantly eliminated by the kidney.

When estimating equations are not expected to provide accurate measures of kidney function (i.e., due to altered creatinine generation or unstable serum creatinine concentrations) and therapeutic drug monitoring is not available, it may be reasonable to obtain an accurately timed urine collection in order to calculate a measured creatinine clearance, particularly for narrow therapeutic window drugs with high toxicity (Figure 5). For example, determining a measured creatinine clearance in patients preparing to initiate therapy with potentially toxic chemotherapeutic regimens may be appropriate. However, there are important caveats to using a measured creatinine clearance for drug dosing purposes. These include the potential for under- or over-collection of urine, which affects the accuracy of the measurement, and a delay in initiating drug therapy due to the time required for urine collection. Thus, measurement of CL_{CR} via a timed urine collection is recommended for individuals in whom renal function estimating equations perform poorly and narrow therapeutic window drugs with high toxicity are to be used (Figure 5).[66]

Summary

The C-G equation has been the most commonly used method to estimate kidney function for drug dosing purposes for years. The advent and widespread clinical use of MDRD derived eGFR has facilitated identification and classification of patients with CKD and now provides clinicians a potential alternative to C-G for drug dosing, but limited data validating its utility in drug dosing currently exists. Neither the C-G nor the MDRD derived kidney function estimate should be used as the sole determinant of drug dosing decisions. Potential discrepancies in kidney function estimates and corresponding drug dosing regimens necessitate careful consideration of the risk-benefit ratio of each approach within the context of the complete clinical picture. Factors that should be considered include the performance of the equation in the specific patient population, the therapeutic index, indication, and toxicity profile of the drug in question, availability of alternative agents, and whether the drug can be titrated to response or dosed using serum concentrations and prospective pharmacokinetic methods. Accurate measurement of CL_{CR} or GFR may be required in some cases. In the future, the FDA will likely require pharmaceutical manufacturers to provide dosing recommendations based on eGFR in addition to C-G CL_{CR} for inclusion in the prescribing information of newly approved drugs. However, the prescribing information of most, if not all, currently approved drugs will continue to be based on CL_{CR} alone, so clinicians must become familiar with the advantages and limitations of using the C-G and MDRD equations in order to provide optimal drug dosing recommendations.

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Figure Legends

Figure 1. Cockcroft-Gault and MDRD Study equations and associated calculations.[1-4] Abbreviations: CL_{CR}, estimated creatinine clearance; SCr, serum creatinine concentration (mg/dL); IBW, ideal body weight; TBW, total body weight; MDRD, Modification of Diet in Renal Disease; AA, African American; BSA = body surface area.

Figure 2. Mean bias by peer group versus isotope dilution gas chromatography mass spectrometry (IDMS) reference measurement procedure for fresh-frozen serum specimen. Error bars indicate 1.96 X SD for distribution of participant results. The error bars that appear missing are smaller than the plot symbol. The numbers on the horizontal axis identify the instrument manufacturer and are in the following sequence: 1, Abbott; 2, Bayer; 3, Beckman Coulter; 4, Dade Behring; 5, Nova; 6, Olympus; 7, Roche; 8, Schiapparelli; 9, Toshiba; and 0, Vitros. Reprinted from [Miller WG, et al. Creatinine Measurement: State of the Art in Accuracy and Interlaboratory Harmonization. *Arch Pathol Lab Med* 2005;129(3):297-304] with permission from *Archives of Pathology & Laboratory Medicine*. Copyright 2005. College of American Pathologists.[24]

Figure 3. Effect of creatinine measurement imprecision on eGFR. *Solid lines* represent the upper and lower limits of the 95% confidence interval for eGFR for a 60 y.o. non–African-American female for whom the eGFR is 60 mL/min/1.73 m^2 at a serum creatinine concentration of 1.00 mg/dL, using a value of 0.06 mg/dL as the measurement standard deviation (SD). This SD was the median SD observed for 50 different method groups assaying a fresh-frozen serum

specimen with a creatinine value of 0.90 mg/dL in the 2003 CAP survey.[24] The *dashed lines* represent the upper and lower limits of the 95% confidence interval for eGFR based on the largest peer-group SD (0.13 mg/dL) observed in the survey. Reprinted from [Myers GL, et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. *Clin Chem* 2006;52(1):5-18] with permission from *Clinical Chemistry*. Copyright 2006. American Association for Clinical Chemistry.[25]

Figure 4. Sample calculations of C-G derived CL_{CR} and MDRD derived eGFR. Abbreviations: TBW, total body weight; IBW, ideal body weight; BSA, body surface area; MDRD, Modification of Diet in Renal Disease equation; eGFR, estimated glomerular filtration rate; C-G, Cockcroft-Gault equation; CL_{CR}, estimated creatinine clearance; SCr, serum creatinine; $MDRD_{IND}$, individualized Modification of Diet in Renal Disease eGFR value (i.e., not normalized for body surface area); C-G_{IBW}, Cockcroft-Gault equation with ideal body weight used for the weight term; C-G_{TBW}, Cockcroft-Gault equation with total body weight used for the weight term.

Figure 5. Proposed algorithm for use of serum creatinine-based kidney function assessments in medication dosing. This algorithm is based on hypothetical clinical scenarios, and has not been validated prospectively. TDM, therapeutic drug monitoring.

Figure 1.

Cockcroft-Gault Equation (C-G)[a,b,c]

- CL_{CR} (mL/min) = [(140-Age) / SCr] x (weight / 72) x (0.85 if female)
- $C\text{-}G_{IBW}$ = IBW used for weight coefficient in C-G equation
- $C\text{-}G_{TBW}$ = TBW used for weight coefficient in C-G equation

Original 4-variable MDRD Study Equation (used with non-standardized SCr)[a]

- eGFR (mL/min/1.73 m^2) = **186** x $(SCr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if AA)

Re-expressed 4-variable MDRD Study Equation (used with standardized SCr)[a]

- eGFR (mL/min/1.73 m^2) = **175** x $(SCr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if AA)

Conversion of BSA normalized MDRD eGFR to an individualized value ($MDRD_{IND}$)[d]

- eGFR (mL/min) = eGFR (mL/min/1.73 m^2) x (estimated BSA/1.73 m^2)

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[a] Age (years)

[b] Weight (kg)

[c] IBW (kg) = (2.3 x inches > 5 feet) + 50 (males), or (2.3 x inches > 5 feet) + 45.5 (females)

[d] BSA = $(\text{weight in kilograms})^{0.425}$ x $(\text{height in centimeters})^{0.725}$ x 0.007184

Figure 4.

Example 1: Average effect of serum creatinine concentration standardization

- 60 y.o. woman, TBW 55 kg

Non-standardized SCr = 1.12 mg/dL

- C-G_{TBW} = 46.4 mL/min

Standardized SCr = 1.0 mg/dL

- C-G_{TBW} = 51.9 mL/min

Example 2: Effect of rounding of SCr

- 85 y.o. caucasian woman, TBW 55 kg, height 62 inches, IBW 50 kg, BSA 1.55 m^2

SCr = 0.7 mg/dL

- MDRD = 85 mL/min/1.73 m^2
- $MDRD_{IND}$ = 76 mL/min
- C-G_{IBW} = 46 mL/min
- C-G_{TBW} = 51 mL/min

SCr rounded to 1.0 mg/dL

- MDRD = 56 mL/min/1.73 m^2
- $MDRD_{IND}$ = 50 mL/min
- C-G_{IBW} = 32 mL/min
- C-G_{TBW} = 36 mL/min

Example 3: Effect of weight/obesity

- 45 y.o., African-American man, height 74 inches, IBW 82 kg, SCr = 3.0 mg/dL

TBW 90 kg, BSA 2.21 m^2

- MDRD = 29 mL/min/1.73 m^2
- $MDRD_{IND}$ = 37 mL/min
- C-G_{IBW} = 36 mL/min
- C-G_{TBW} = 40 mL/min

TBW 140 kg, BSA 2.66 m^2

- MDRD = 29 mL/min/1.73 m^2
- $MDRD_{IND}$ = 45 mL/min
- C-G_{IBW} = 36 mL/min
- C-G_{TBW} = 62 mL/min
