THE RIGHT DOSE:

Leveraging Technology and Tools to Optimize Renal Dosing

A lack of precision

The term "precision dosing" has caught on in recent times as a way to tailor a drug dose to an individual patient. Although the term has been used recently to describe dose adjustments based on a patient's genomics, the data available to clinicians regarding genomic dosing is limited and most precision dosing has to do with adjusting doses for body size and kidney/liver function. It has long been known that patients with impairment in kidney function require reduced doses of drugs that are substantially eliminated by the kidney. However, it is impractical to measure kidney function in routine practice and so equations that are used to estimate kidney function have been developed. These equations are not precise—they suffer from significant limitations and are not interchangeable, making the process of properly dose adjusting drugs a complex one. However, pharmacists have been at the forefront of selecting and interpreting these equations and armed with effective clinical decision support and surveillance tools, are able to make individualized dosing decisions that will optimize drug therapy for their patients.

A history of FDA guidance regarding kidney function estimating equations

Prior to 1998, there was no industry guidance about how pharmacokinetic studies should be conducted in patients with kidney impairment. What we knew about dose adjusting medications came from post-approval studies conducted by clinician investigators. These studies often utilized a limited number of patients, and so results lacked external validity and there were often conflicting recommendations depending on which source was consulted.[1]

In 1998, the United States Food and Drug Administration (FDA) approved the first Guidance for Industry, which discussed when a pharmacokinetic (PK) trial should be performed in subjects with kidney impairment, strategies for trial design and implementation, data analysis and a more standardized way to present the results of PK trials, and recommended dose adjustments in the product labeling (US FDA 1998). The 1998 Guidance suggested that creatinine clearance was the preferred measure of kidney function as it is "used widely in patient care settings" and mentions the Cockcroft-Gault equation as a formula often used to estimate creatinine clearance based on serum creatinine levels.

The Cockcroft-Gault equation

The Cockcroft-Gault equation was developed in 1976 from 249 people, 96% of whom were male.[2] It estimates creatinine clearance using a patient's age, serum creatinine, sex, and weight and is the equation with which we have the most clinical experience. It does, however, have important limitations. It is a predictor of creatinine clearance, and because creatinine is not only filtered by the kidneys, but secreted as well, it tends to overestimate glomerular filtration rates (GFRs) by an average of ~15%, with larger errors in patients of larger body size.[3] Furthermore, an unstandardized creatinine assay was utilized, for which the details are no longer available, making it impossible to apply any correction factor for use with modern assays.[4]

The Cockcroft-Gault also suffers from the limitations of using any serum creatinine-based equation. For example, in order to be accurate, the serum creatinine must be at steady state. Furthermore, as creatinine is influenced by muscle mass, it loses accuracy in patients at the low and high extremes of body weight and/or muscle mass. Clinicians have utilized various correction factors (e.g., substituting ideal or adjusted body weights into the equation for patients with obesity, rounding the serum creatinine upwards for patients of low body weight) in an attempt to improve estimates, but there is variability in the use of these correction factors as well.[5]

2010 industry guidance

After the FDA guidance was published in 1998, there was a significant improvement in the number of pharmacokinetic studies and recommendations for dose adjustments in kidney impairment provided in manufacturer labeling for drugs submitted for FDA approval. From 1999 to 2010, pharmacokinetic studies enrolling subjects with kidney impairment were conducted in 71.6% of new drugs, as opposed to only 56.3% conducted from 1996 to 1997.[1] A new FDA guidance was introduced in 2010, which stated that "either the Cockcroft-Gault or Modification of Diet in Renal Disease (MDRD) equations can be used to assign subjects to a renal impairment group," which introduced additional complexities for clinicians as now drug recommendations could be made using two different methods.[6]

The MDRD equation

The MDRD equation was first introduced in 1999 using data collected from 1600 subjects with chronic kidney disease (CKD) who were participating in a study looking at whether

interventions such as protein restriction could slow the progression of kidney impairment.[7] The equation utilizes age, serum creatinine, sex, and race (Black or White Americans) to estimate GFR. Although it still suffers from the same limitations of a serum creatinine-based equation, when it was published it was the most accurate estimator of GFR available (although over 10% of results still deviated more than 30% from measured GFR) and became routinely reported by laboratories as a way to identify patients with CKD.[4]

Because of its improved accuracy and easy accessibility on laboratory reports, the MDRD became an appealing equation to apply to drug dosing. However, this equation does suffer from significant limitations when used for that purpose — because it was developed in individuals who already had CKD, it significantly loses accuracy in patients with GFR > 60 mL/minute/1.73m^2, which is clinically important as patients will still potentially need drug dose adjustments at higher levels of GFR. Additionally, the MDRD reports an estimated GFR (eGFR) that is normalized to a patient's body surface area (BSA). This can be detrimental in drug dosing because a large person will generally have larger kidneys and a higher raw GFR (in mL/min) than a smaller person. Hence, using the MDRD equation to dose drugs will lead to an underestimation of GFR in patients of large body size, and overestimation of GFR in patients of low body size, unless the BSA normalization is reversed prior to making drug dosing evaluations.[3,4] However, the 2010 FDA guidance recommended reporting MDRD-related dosing recommendations using the GFR still normalized to BSA (mL/minute/1.73m^2).[6]

Beyond 2010

In the pharmaceutical industry there has been a clear shift away from the Cockcroft-Gault equation toward the MDRD since the 2010 guidance for industry was published with 16.7%, 70%, and 46.7% of new drug labels providing recommendations based on the MDRD equation in 2015, 2016, and 2017, respectively.[3] This has led to some considerable variability in kidney function measurements some of which is not even readily apparent to the clinician. For example, in the case of the antibiotic delafloxacin, which was approved in 2017, phase I PK trials grouped patients with kidney impairment utilizing the MDRD, but phase 2 & 3 trials excluded patients based on the Cockcroft-Gault calculation. Ultimately, the FDA used pooled phase 3 data that used Cockcroft-Gault (using ideal body weight normalized to BSA) but because that permutation of the Cockcroft-Gault equation correlated more highly with the MDRD equation than it did with the standard Cockcroft-Gault equation, the MDRD was chosen for the final dose adjustments recommended that in the package insert. The correlation was high (0.86) but not exact, emphasizing the fact that normalizing a CrCl to BSA will produce matching units, but the results cannot necessarily be assumed to be interchangeable.[3]

A new draft guidance for industry for subjects with kidney impairment was posted in September 2020. In this document, CrCl and eGFR are still recommended, although two equations were now cited as options for reporting eGFR — the MDRD or CKD-EPI equations.[8]

The CKD-EPI equation

The CKD-EPI equation was developed in 2009 and used data from several different trials so that over 8,000 subjects from a variety of different centers are included.[9] The CKD-EPI equation is an improvement over the MDRD equation, especially at eGFR levels greater than 60 mL/minute/1.73m[2], and has been reported to perform better than both the Cockcroft-Gault and MDRD in studies of aminoglycoside clearance.[10,11] It still has the same limitations of using serum creatinine as a marker of kidney function that the Cockcroft-Gault and MDRD have, and is normalized to body surface area, meaning that just like with the MDRD equation it will also underestimate kidney function in large individuals and overestimate kidney function in small individuals when the normalization is not undone. However, with the incremental improvements provided by the CKD-EPI equation, some experts are hopeful that this equation will provide an opportunity to make the CKD-EPI the standard estimating equation.[3,4] The estimate would need to be denormalized, at least for patients on the extremes of body size, and this is starting to be recognized by the FDA. Indeed, the new draft guidance document contains a discussion regarding the importance of individualizing the eGFR estimates for drug dosing by multiplying the standardized GFR by the BSA and dividing by 1.73. Perhaps this approach, if it can catch on in clinical practice as well, will ultimately provide a much-needed standardized approach to drug dosing.

On the horizon — removing race from eGFR-estimating equations

One additional aspect of drug dosing equations to watch carefully has to do with a reevaluation of the inclusion of race in the MDRD and CKD-EPI equations. Race currently is a variable in the equations because it improved the accuracy of the equation. However, the uncertainty of an individual eGFR value predicted by the equation is large enough that there is considerable overlap in uncertainty between Black and non-Black individuals, and so the value of increasing the estimate by 16% in Black individuals has been called into question.[12] Because these equations are not very precise in the first place, it is harmful to make adjustments for the social construct of race, as these estimates impact everything from drug dosing, to when a patient is referred to a nephrologist, to when patients can receive a kidney transplant. On March 9, 2021 the American Society of Nephrology and National Kidney Foundations issued an update from their joint Task Force on "Reassessing the Inclusion of Race in Diagnosing Kidney Diseases" informing patients that they are hoping to issue a full report in the coming months, ideally finding a suitable approach

that is accurate, non-raced based, and standardized.[13] If this new approach can also be applied to drug dosing, this may modify the equations that are being utilized for kidney function estimates.

Clinical Practice Implications

As governing societies evaluate the need for change from a global perspective related to more specific and inclusive calculations, clinical pharmacists are actively engaged in practice across the United States working to ensure that patient therapy is optimized.

It is estimated that as of 2019, there are 81,000 pharmacists practicing in hospitals throughout the United States.[14] While all pharmacists are not nephrology specialists, nearly every pharmacist must examine medication regimens and provide renal dosing recommendations as appropriate. Pharmacists have a tremendous impact in ensuring the safe and effective delivery of medications beyond dispensing, which is critical for the renal population.

Areas of emphasis that impact renal dosing therapy include the following:

- Providing medication consultative services to clinical teams
- Providing drug information to families, physicians, and nurses
- Monitoring therapeutic response of narrow therapeutic index drugs
- Medication Reconciliation across a continuum
- Monitoring for adverse drug events
- Participating in the development of treatment protocols
- Requesting and monitoring laboratory data

Clinician teams are faced with the challenging process of evaluating patients' medication regimens throughout the duration of a hospital admission. The optimization of medication dosing must be personalized, especially in light of the increasing complexity of the patient population. It is key to encompass the complete patient assessment, which includes determining the appropriateness of therapy, and dose adjustments for renal and hepatic function. Pharmacists are expected to work as partners with our nursing and

The five rights of medication administration

To reduce medication errors and harm, it is recommended to use the five rights of medication administration.

1 | THE RIGHT **PATIENT**

2 | THE RIGHT **DRUG**

3 | THE RIGHT **DOSE**

4 | THE RIGHT **ROUTE**

5 | THE RIGHT **TIME**

physician colleagues to practice the "five rights" of medication administration. Ensuring each patient has the "right dose" often involves an assessment to determine the need for dose adjustments, medication timing and drug interaction avoidance.

Pharmacists are making these complex decisions regarding renal dose adjustments on a daily basis. Over 1 in 5 hospitalized patients develops acute kidney inury (AKI)[15] and approximately 50% of the intensive care population will experience AKI while admitted, requiring a more comprehensive appraisal of their medication regimens.[16]

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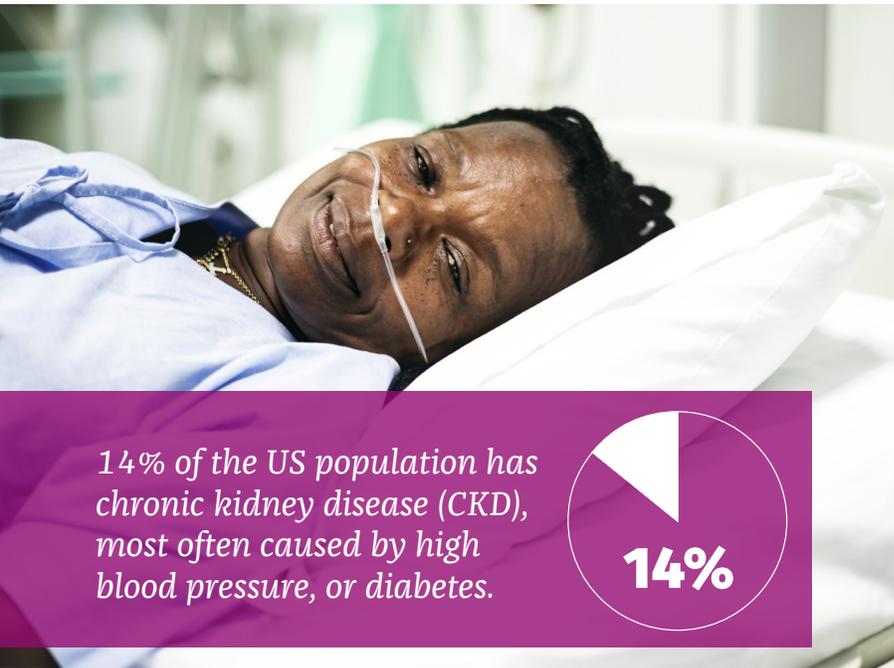
Approximately, 14% of the US population has chronic kidney disease (CKD), most often caused by high blood pressure, or diabetes.[17] Certain medical comorbidities (systemic infections, obesity, autoimmune diseases), race and age increase the risk and progression of CKD. Due to the intricacy of the patient population, medication dose adjustments are necessary due to alterations in pharmacokinetic and pharmacodynamic parameters such as alterations in protein binding and decreased drug elimination. Patients with advanced CKD (Stages 3-5) often present with numerous comorbid conditions and an average of ten medications requiring 20-30 medication doses daily. [18,19,20,21]

Pharmacists are experts in examining dosing regimens and making dose recommendations based on an individual's estimated GFR. Historically, those adjustments have been conducted with the use of the Cockcroft-Gault formula. As science evolves, we continue to take a more personalized approach to therapy. Moving forward in clinical practice, we are utilizing formulas such as MDRD and/or CKD-EPI in various populations. Clinical judgement is imperative when assessing dosing regimens for patients that are obese or of advanced age, and particular attention should be paid to patients with fluctuating serum creatine during hospitalization, since all three equations require serum creatinine to be at steady state and significantly lose accuracy in patients with acute kidney injury.

The ability to incorporate multiple ways to estimate kidney function in our hospital databases is imperative. Let's examine a brief case study. In the case study on this page an individual patient may have different dose recommendations for the same medication if the clinician is unaware of and/or using the inappropriate updated calculation to modify drug dosing. Clinical surveillance software monitors patient data in the EHR to prioritize patients in real time at risk to detect these types of changes through a hospital stay, and to provide individual clinicians with evidence-based recommendations.

CASE STUDY

- Patient: 73 year old, African American female, with diabetes mellitus and hypertension.
- Medications: Valsartan 160 mg daily, Hydrochlorothiazide 25 mg daily, Metformin 1000 mg twice daily
- Weight: 82 kg, 64 inch, SCr 1.4 mg/dL
- Renal Function Estimate: eGFR: 43 mL/min/1.73m^2

Prior to 2016, Metformin would need to be discontinued in this patient, as it was contraindicated in patients with a SCr above 1.4 or 1.5 mg/dL, depending on if the patient were female or male, respectively, due to concerns for the potential of Metformin accumulation leading to lactic acidosis. However, because lactic acidosis is rare, and utilizing SCr values is an inaccurate way to measure kidney function, the FDA revised their warnings so that Metformin can be used in patients with mild kidney impairment (eGFR > 45 mL/min/1.73m^2 and in some patients with moderate kidney impairment (eGFR 30 to 45 mL/min/1.73m^2).[22] In this patient with an estimated eGFR of 43 mL/min/1.73m^2, assuming that her SCr is at baseline (i.e. she is not experiencing acute kidney injury), the patient could continue to benefit from Metformin therapy, just at a reduced dose (500 mg twice daily) of the medication.

As the FDA increases the number of newly developed medications that will utilize GFR estimating equations, bedside pharmacists will need to assist in this transition at the local level where needed. This transition may include a review of hospital approved renal dosing protocols and/or therapeutic interchange programs. Several of the medications used to treat diabetes and various cardiovascular diseases are included in the listing of products that may have updated monographs.

Medications with Renal Dosing using eGFR categories

Hyperglycemic Agents	Cardiac Agents	Antimicrobials/ Antivirals
Sitagliptin	Gemfibrozil	Remdesivir
Saxagliptin		Meroponem and Vaborbactam
Dapaglafozin	Spironolactone	Delafloxacin
Canagliflozin	Eplerenone	
Metformin	Sacubitril and Valsartan	

Leveraging Technology to Improve Patient Safety

Health systems depend upon internal systems of checks and balances to ensure the safety of patients in such a vulnerable position. These systems may include the use of electronic health records (EHRs) and/or clinical decision support (CDS) platform, like Lexicomp, and clinical surveillance solutions, like Sentri7, to ensure up to to date, quality care while minimizing adverse drug events. ASHP Best Practices encourages the use of CDS to increase patient safety and improve the efficiency of our medication delivery process.[23] Kidney Disease Improving Global Outcomes (KDIGO) and the National Kidney Foundation (NKF) publish several guidelines and various digital assets that may be used to manage many of the comorbidities associated with CKD as well.[24,25] **It's imperative that clinicians have the most up to date information enabling safe and effective medication therapy.**

As the clinical state of an individual patient shifts during an admission, pharmacists must be nimble in their approach. In addition to renal dose adjustments conducted during initial order verification, opportunities for de-escalation/discontinuation of unnecessary and/or potentially harmful medications must be conducted as well. **The use of real-time clinical surveillance software is pivotal in helping to identify these scenarios, thereby improving patient outcomes.**

EHRs and their accompanying clinical decision support systems typically provide suggestions regarding drug interactions at the point of order entry and the initial order verification. Real-time surveillance software alerts clinicians on an ongoing basis to changes in key health information such as vital signs, medication and laboratory data that may adversely affect patient care. This reduces time to discovery of an adverse event.

In this instance, real-time surveillance can also help to identify nephrology patients with orders and or administration of Renin-Angiotensin-Aldosterone System (RAAS) agents with electrolyte abnormalities requiring immediate attention that can prove to be consequential if left unaddressed. Other common examples include overuse or inappropriate use of NSAIDS in AKI/CKD, and the continuation of Proton Pump Inhibitor (PPI) therapy as part of protocols although not indicated in each patient. Leveraging technology to maintain closer monitoring in this population as they receive anticoagulant therapy may prove to be lifesaving.[26]

Conclusion

Clinical pharmacists serve an invaluable role in the management of patients within the inpatient hospital setting. This is especially important when caring for patients that have complex disease states often presenting with polypharmacy at increased risk of morbidity and mortality.

As clinical evidence continues to emerge, clinical teams will need to make necessary adjustments to take an inclusive approach to treating patients to avoid unintended consequences of established methods of patient assessment and drug dosing.

The use of technology via clinical decision support tools and or surveillance tools will prove to be invaluable as busy teams of pharmacists work to manage increasing patient workload and keep abreast of changes in medical literature. The proper care of vulnerable and at-risk populations will often require clinical judgement in concert with the use of technological resources to advance patient care.

WOLTERS KLUWER SOLUTIONS ARE UPDATING RENAL DOSING PROTOCOLS TO SUPPORT EGFR GUIDELINES

At Wolters Kluwer, we are striving to deliver solutions that account for both knowledge and workflow to help optimize care for patients, especially those at high-risk of complications. Our goal is to deliver confidence that you, your team, and your organization are making the right decisions to improve the lives of patients.

As your trusted partner, Wolters Kluwer is paying careful attention to the new and evolving evidence and updating our expert-driven tools, UpToDate, Lexicomp, and Sentri7, accordingly.

Lexicomp

Our expert team is updating renal dosing field recommendations based upon the best available evidence and clinical expertise. Our collaborative group of pharmacokinetic and clinical experts works to provide clinicians with the most up-to-date and clinically relevant information enabling safe and effective medication therapy. These updates aim to provide clear and concise recommendations to clinicians at the bedside, as well as recommendations for dosing in patients receiving different types of dialysis therapies, like hemodialysis, peritoneal dialysis, continuous renal replacement therapy and prolonged intermittent renal replacement therapy, so that dosing can be as tailored to some of our most complex patients.

Sentri7

Sentri7 supports pharmacy teams proactively monitoring patients based on renal dosing rules and generates alerts when interventions are needed, so they are equipped to consistently deliver the highest quality, evidence-based care. Sentri7 makes it easy to standardize renal dosing protocols across facilities to ensure consistent, high-quality care.

With Sentri7's Pharmacy Analytics dashboard, track key metrics and increase the pharmacy teams' impact on hospital- or system-level performance. The dashboard's robust reports transform data into essential insights for revising policies or educating prescribers. Compare prescribed medications across facilities to ensure compliance with current health system priorities, identify high and low performers and track cost savings tied to interventions.

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