Estimating Renal Function for Drug Dosing: Rewriting the Gospel?

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INTRODUCTION

One of the hospital pharmacist's many clinical roles is to estimate renal function, refer to literature references, and adjust medication doses for renal dysfunction. Use of the Cockcroft–Gault (CG) equation for this purpose has long been pharmacists' "11th commandment". Recently, however, the increasing availability of estimates of glomerular filtration rate (GFR) from clinical laboratories has led some to call for this commandment to be rewritten.[1-3] In this paper, we examine this issue and give readers a suggestion for what we think the "new gospel" should entail.

IN THE BEGINNING

The basis for most of today's renal drug dosing (i.e., dosage adjustments made according to renal function) was described in the 1970s. The relation between renal function and drug clearance was first described by Tozer.[4] Clinicians then required a way to estimate renal function, and Levy[5] was the first to use creatinine clearance to estimate renal function for the purpose of drug dosing. So-called renal drug dosing then proceeded, with creatinine clearance being used to estimate renal function. In 1980 Bennett and others[6] compiled a list of suggested drug dosage adjustments based on the fraction of the drug cleared renally and an estimate of the patient's renal function. These dosage adjustments are now compiled in a commonly used reference book.[7] The *Compendium of Pharmaceuticals and Specialties*[8] refers to the CG equation, and most product monographs within that resource include recommended dosages for renal dysfunction.

Clinicians need to be aware that using serum creatinine as a marker of renal function has limitations. The renal function of hospitalized patients may change rapidly, and a serum creatinine value at one point in time may not accurately reflect the patient's present status; rather, it may reflect renal function over the past day or so. Serum creatinine levels can also be affected by muscle wasting, high-protein meals, a vegetarian diet, or fasting.[9] As well, the formula is relatively insensitive for detecting changes in renal function for patients with near-normal serum creatinine. However, this limitation has minimal clinical relevance for the current discussion, as relatively small changes at this level are unlikely to affect drug dosing. Finally, for patients using any type of dialysis, serum creatinine cannot be used as a marker of renal function for drug dosing.

THE "OLD TESTAMENT"

As mentioned above, in 1972, Cockcroft and Gault published a formula to estimate creatinine clearance using the patient's age, weight, and serum creatinine level; this formula (Equation 1 in Appendix 1) became the "11th commandment" and one of the most commonly used tools in hospital pharmacists' practice.[10] The equation was developed with data collected from a group of 249 men, 18 to 92 years of age, with stable serum creatinine,[10] factors that potentially limited its generalizability. Because the formula was derived solely from data obtained from men, a 15% adjustment for women was added to correct for the relative difference in the amount of fat and muscle between the sexes; this adjustment was not based on female-derived data.[11]

BLASPHEMY?

Although not always stated, renal drug dosing recommendations are based on comparisons of relative (not actual) renal function. In other words, they should be based on the degree of renal function of the patient

in question in comparison with a "normal" patient (i.e., a 70- kg man). Clinicians should be aware that when using the original CG equation, which includes a weight variable, the resulting estimate (in mL/min) reflects the patient's actual renal function. However, for dosing adjustments, clinicians should instead use an estimate of the patient's relative renal function (in mL min^{-1} 70 kg^{-1} or mL min^{-1} 1.73 m^{-2}). A modified version of the CG equation (Equation 2 in Appendix 1) calculates creatinine clearance standardized to a 70-kg man.

Drug dosing based on actual or relative creatinine clearance has not been compared for efficacy or toxicity outcomes, but basic pharmacokinetic principles explain why it makes sense to leave out the weight variable when assessing renal function for the purposes of drug dosing.[12] Whereas the total daily dose of a medication is based on the overall systemic clearance of the drug, changes to the dosing interval should be made on the basis of relative half-life differences. The half-life is in turn based on the ratio of volume of distribution and systemic clearance (Equation 3 in Appendix 1). Smaller patients will obviously have lower clearance rates (mL/min) than larger patients (because they have smaller kidneys), but they will also have smaller volumes of distribution. Thus, the half-life for a smaller individual (with a lower clearance, measured in mL/min) should be similar to that for a larger individual. Including body weight in creatinine clearance formulas will result in lower values for smaller individuals; it will thus inappropriately underestimate their renal function and could potentially lead to unnecessary extensions of the dosage interval.[12]

THE "NEW TESTAMENT"

In 1999 the Modification of Diet in Renal Disease (MDRD) study equation (Equation 4 in Appendix 1) was developed by applying multiple regression to patient-specific data from 1070 patients with renal disease and measurements of iothalamate labelled with iodine-125.[13] The equation was subsequently validated in another 533 patients from the same population.[13] Notice that the resultant GFR is reported as milliliters per minute per 1.73 m^2 body surface (mL min^{-1} 1.73 m^{-2}) not millilitres per minute (mL/min) (see the section entitled "Blasphemy", above).

The equation that many laboratories now use to report estimated GFR is the abbreviated MDRD equation (Equation 5 in Appendix 1), which requires only serum creatinine and demographic variables.[14] Similar to the CG equation, the new MDRD formulas still require that patients' renal function be at steady state to get the most accurate assessment of renal function. As well, the MDRD equations were designed to be used as diagnostic tools— screening the population for renal dysfunction— and not for drug dosing.

THE NEW TESTAMENT VERSUS THE OLD TESTAMENT

The National Kidney Foundation has recently reviewed the literature related to the predictive performance of these equations for GFR, as measured by iothalamate or iohexol clearance. For the CG equation, the proportion of estimates within 30% of actual (measured) GFR ranged from 48% to 95%.[15] The full MDRD equation yielded better predictions, with 88% to 91% of GFR estimates being within 30% of measured values.[15] The abbreviated MDRD equation performed almost as well as the full MDRD equation, with 84% to 91% of GFR estimates within 30% of measured values.[15] One of the reasons that the MDRD equations perform better than the CG equation in these situations is because they were designed to estimate GFR, whereas the CG equation was designed to estimate creatinine clearance.[10,13]

Recently, Wargo and others[16] found that rates of antimicrobial dosage discordance (differing dose recommendations) between doses based on the CG equation and those based on the MDRD equations ranged from 21% to 37%. The majority (86%) of the discordances occurred when the estimate from the CG equation dictated a dosage adjustment but the estimate from the MDRD equations did not.[16] The authors stated that the patients would have been "overdosed" 21% of the time if the MDRD equation had been used.[16] However, because the authors did not look at any clinical parameters to assess proper dosing, it is probably more appropriate to simply state that the doses would have been different. In addition, the assumption that the dose determined by the CG equation is correct is just that: an assumption. There is little if any evidence showing that doses calculated this way are clinically correct.

de Lemos and others[17] examined the impact of using the abbreviated MDRD and CG equations in calculating carboplatin doses with the Calvert equation (Equation 6 in Appendix 1). For all patients, actual GFR was measured with diethylenetriaminepenta-acetic acid labelled with technitium-99m for comparison.[17] Use of either of the 2 equations to estimate GFR would have led to lower doses than if the measured GFR values had been used (doses of 622 mg by measured GFR, 557 mg

by the CG equation, and 575 mg by the abbreviated MDRD equation). There was no statistically significant difference in GFR estimates between the CG and abbreviated MDRD equations (p = 0.68).[17] Even if the 18-mg (3%) difference in calculated dose between the 2 equations was real, it is unlikely that it would produce a clinically important difference. The discrepancy between the doses calculated with measured and estimated GFR is not surprising, as the Calvert equation causes the dose of carboplatin to change in direct proportion to renal function, whereas most drug dosing tables have broad categories. Although de Lemos and others used the Calvert equation as the reference equation, there was no way to determine the "correct" dose for these patients.

Most recently, Gill and others[18] examined differences between GFR estimates for elderly patients in long-term care centres and described the effect of these estimates on dosing of 2 medications, amantadine and digoxin. For 180 patients, the mean GFR estimates were 72.9 mL min^{-1} 1.73 m^{-2} with the abbreviated MDRD equation and 52.1 mL min^{-1} 1.73 m^{-2} with the CG equation.[18] With the abbreviated MDRD equation, 21.2% fewer patients would have received an amantadine dosage reduction and 32.2% fewer patients would have received a digoxin dosage reduction. The authors acknowledged that the "correct" dose was undetermined and recommended "caution" when using these formulas for drug dosing.

WHICH TESTAMENT SHOULD WE FOLLOW?

Various opinions on this topic have been expressed by pharmacy's "disciples", and one must carefully consider the underlying beliefs in an effort to get at the "truth".

Belief 1: Because the MDRD equation is more accurate, it should be used for drug dosing.

Bailie and others[19] were the first to state that pharmacists should switch to the MDRD equations because, according to data from the National Kidney Foundation, they were more accurate. However, the need for a more accurate test depends entirely on how the result will be used. Estimates of renal function, when used for dosage adjustments, are typically used in conjunction with drug dosing tables that have broad categories. For example, *Drug Prescribing in Renal Failure*[7] and *The Sanford Guide to Antimicrobial Therapy*[20] both use GFR categories of greater than 50, 10–50, and less than 10 mL/min for dosage recommendations. The product monograph for ciprofloxacin divides renal function into 2 categories (31–60 and less than 30 mL min^{-1} 1.73 m^{-2}) and provides maximum daily dosages for each.[21] These categorizations have been set somewhat arbitrarily and are almost never based on a pharmacodynamic evaluation of the clinical impact of the dosing recommendations. Furthermore, they are also only loosely based on pharmacokinetic principles. When medications are marketed, the doses are rounded off to convenient amounts (e.g., 1000 mg instead of 875 mg) and intervals (q8h, not q9h or q5h). The use of tables and rounding of doses and intervals produces far greater variation in the dose received than almost any differences that would be caused by different estimates of renal function.

Belief 2: The MDRD equations should not be used because the manufacturers' recommended dosage adjustments are based on the CG equation; using a different formula than the one traditionally used by manufacturers will lead to errors in dosage adjustments.

In a commentary in *Pharmacotherapy*, Bauer[2] stated that pharmacists should not switch to GFR estimation equations (such as the MDRD equations), noting that most pharmacokinetic studies done to create renal dosing recommendations have used estimates of creatinine clearance, not GFR, as per guidelines from the US Food and Drug Administration. In July 2006, the National Kidney Disease Education Program issued a statement[22] recommending that pharmacists continue to use current dosing practices (i.e., with the CG equation) because the impact on drug dosage adjustment with the MDRD equation had not yet been examined. In a recent article, Spruill and others[23] provided a comprehensive review of the use of the MDRD equations for drug dosing, concluding that pharmacists should continue to use the CG equation, as this formula had provided the framework for drug dosing research and recommendations.

In a systematic review, Vidal and others[24] examined 4 drug information sources and found "remarkable variation in definitions and recommendations". They concluded that available resources were "ill suited for clinical use".[24] The editors of the drug information sources responded that, because of a lack of regulatory requirements for renal dosing studies[25] and the myriad clinical factors involved,[26] drug prescribing in renal failure "remains imprecise," relying on "interpolation, extrapolation, and estimation".[27] In particular, the editor of *Drug Prescribing in Renal Failure* stated that dosing

for older drugs is based on "flimsy data, such as case reports, common practice, and pharmacokinetic extrapolation from patients with normal renal function".[27] In addition to these points, pharmacists must be mindful that most recommendations for dosage adjustment have never been evaluated pharmacodynamically to determine if the adjusted doses produce the same benefit and carry similar potential for harm.

Belief 3: The MDRD equation should not be used because it has not been validated for drug dosing purposes.

Wolowich and others[3] have pointed out that the MDRD equation has never been validated for the purposes of drug dosing and so would be an inappropriate replacement for the CG equation. While this is technically correct, to our knowledge the same is true for the CG equation. The fact that it was the first equation used for this purpose does not make it the "correct" equation.

Belief 4: The MDRD equation should not be used because it reports relative renal function (units of mL min^{-1} 1.73 m^{-2}) rather than actual renal function (units of mL/min).

Wolowich and others[3] also argued that if the MDRD equation is used, "dosing errors will occur" because of the units (mL min^{-1} 1.73 m^{-2}, rather than mL/min). These authors state that drug dosage recommendations should use individualized GFR estimates (mL/min, not mL min^{-1} 1.73 m^{-2}), and the MDRD results must therefore be multiplied by the patient's body surface area to achieve the correct value.[3] However, as discussed above (see the section entitled "Blasphemy"), using relative renal function estimates is probably the more pharmacokinetically correct way to adjust dosing intervals.

THE "GOSPEL" OF PATIENT ASSESSMENT

We feel that any potential new "gospel" for pharmacists should not be based on the debate between the CG and MDRD equations, but rather should focus on enhancing the overall approach to drug use and dosing assessment in individual patients. In our experience, too many pharmacists make dosing recommendations according to an assessment of renal function alone, rather than relying on the overall clinical picture.

Clinical factors are arguably the most important determinants of whether a dose is "appropriate" for a particular patient. In addition, chronic renal insufficiency can create pharmacokinetic changes (e.g., in volume of distribution or methods of elimination) that further complicate renal drug dosing, which makes the clinical parameters all the more important.[11] Calculated estimates of renal function do not take these factors into consideration, so adjusting doses solely on the basis of renal function estimates may lead to inappropriate recommendations.

Assuming that the drug selected is the correct drug for the patient, with an appropriate balance of efficacy and toxicity, the next assessment should be a determination of the acuity of the patient's situation. If an immediate response is not required, and the dose can be titrated to response, then assessment of renal function is almost unnecessary. The patient should be started at a dose lower than that typically recommended, and the dose should be modified according to response and/or toxicity. For instance, if an angiotensin-converting enzyme inhibitor such as lisinopril (primarily eliminated by the kidneys) is being used to treat high blood pressure in a renally impaired patient, it would be reasonable to start with one-quarter to one-half of the typical starting dose (i.e., one-quarter of a 5-mg tablet) and increase the dose as needed.

If an immediate effect is required, one should attempt to obtain a therapeutic response within minutes to hours, regardless of renal function. This can be accomplished by administering a loading dose or by starting with a regular dose and reducing the dose accordingly once a response has been observed. Use of this method depends on the medication in question and its potential toxic effects. For example, for a patient needing ceftazidime, a relatively nontoxic medication, the initial dose decision is whether to administer 1 or 2 g. If the patient has a life-threatening infection, it would make sense to start with 2 or 3 doses of 2 g each, and then (particularly if a response has occurred) reduce the total daily dose, using the patient's renal function to guide selection of a reasonable dosing regimen. However, pharmacists should be mindful of medications with well-known dose-related side effects, such as aminoglycosides. In patients with renal dysfunction, potentially nephrotoxic medications such as aminoglycosides should be avoided wherever possible, and safer alternatives should be used instead. For medications with a narrow therapeutic index, an overall assessment of the patient's renal function, and of the potential benefits and harms associated with the medication, is needed. If the potential benefits outweigh the potential harms, the pharmacist should make an informed dosage recommendation but should be meticulous in monitoring for adverse events. Finally, if a clinical trial has shown that a specific dose is effective and safe for patients with renal insufficiency, this

evidence should supersede empiric dosing recommendations.

If dosages are based on clinical parameters as well as on renal function estimates, the clinical impact of any miscategorization resulting from the use of dosing tables will be minimized. An antibiotic dose that is too low for the patient may be apparent from persistence of fever, elevation of white cell count, or persistence of positive culture results. Similarly a dose that is too high will be apparent because of adverse effects. For medications with delayed adverse effects or adverse effects that are difficult to monitor, pharmacists should remain proactive in considering dosage adjustment with changes in renal function. They should also be aware that a lack of efficacy and/or the occurrence of toxic effects can occur even at recommended doses; again, the clinical picture remains more important when it comes to dosing recommendations than doses empirically chosen on the basis of renal function estimates.

THE "NEW GOSPEL"

In summary, evidence is available to show that dosages may differ depending on which method of assessing renal function is used, but no studies have shown which method provides "correct" estimates for clinical dosing, probably because no dosage estimate is "wrong". Estimates are by definition imprecise, and the clinical significance of dosage adjustments can be determined only after the dose has been given.

Whether any of the equations discussed in this article is superior for predicting appropriate dosage adjustments remains to be determined. Clinicians should therefore make sure that they understand the difference between absolute and relative renal function, and should use renal function assessments only in conjunction with clinical assessments.

Choosing the initial dose is really only a small part of the work that a pharmacist needs to do. Monitoring the patient's response to the medication is the best way to evaluate if the dose is appropriate and should be the pharmacist's primary role in renal drug dosing. Indicators of efficacy and toxicity should be followed, and dosage changes should be made according to these factors, in addition to serum creatinine, estimated GFR, and literature recommendations. Proactively determining rational starting doses and monitoring a patient's response to the dose chosen should be the new gospel for pharmacists who adjust drug dosages on the basis of renal function. If they do so, the debate about which formula to use could seem somewhat trivial.

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Appendix 1. Equations Relevant to Discussion of Renal Drug Dosing

Equation 1: Original Cockcroft–Gault (CG) equation[11]

$CrCl\ (mL/min) = [(140 - age) \times weight(kg)]/[72 \times SCr(mg/dL)]$
For women, multiply the result by 0.85

CG equation using SI units:
$CrCl(mL/min) = [(140 - age) \times weight(kg) \times 1.2]/SCr(\mu mol/L)$
For women, multiply the result by 0.85

Equation 2: Modified CG equation[13]

$CrCl\ (mL\ min^{-1}\ 70\ kg^{-1}) = (140 - age)/SCr(mg/dL)$

Modified CG equation using SI units:
$CrCl(mL\ min^{-1}\ 70\ kg^{-1}) = [(140 - age) \times 90]/SCr(\mu mol/L)$

Equation 3: Relation between clearance (Cl), volume of distribution (V_d), and half-life ($t_{1/2}$)

$t_{1/2}/0.693 = V_d/Cl$

Equation 4: Modification of Diet in Renal Disease (MDRD) equation[14]

$GFR(mL\ min^{-1}\ 1.73\ m^{-2}) = 170 \times [SCr(mg/dL)]^{-0.999} \times age^{-0.176} \times [BUN(mg/dL)]^{-0.170} \times [Alb(g/dL)]^{0.318}$
For women, multiply the result by 0.762
For blacks, multiply the result by 1.18

MDRD equation in SI units:
$GFR(mL\ min^{-1}\ 1.73\ m^{-2}) = [15\ 028/SCr(\mu mol/L)]^{-0.999} \times age^{-0.176} \times [BUN(mmol/L)/0.357)^{-0.170} \times [Alb(g/L)/10]^{0.318}$
For women, multiply the result by 0.762
For blacks, multiply the result by 1.18

Equation 5: Abbreviated MDRD equation[15]

$GFR(mL\ min^{-1}\ 1.73\ m^{-2}) = 186.3 \times [SCr(mg/dL)]^{-1.154} \times age^{-0.203}$
For women, multiply the result by 0.742
For blacks, multiply the result by 1.21

Abbreviated MDRD equation in SI units:
$GFR\ (mL\ min^{-1}\ 1.73\ m^{-2}) = 186.3 \times [SCr(\mu mol/L)/88.4]^{-1.154} \times age^{-0.203}$
For women, multiply the result by 0.742
For blacks, multiply the result by 1.21

Equation 6: Calvert equation[18]

$Dose\ (mg) = AUC(mg\ mL^{-1}\ min^{-1}) \times [GFR(mL/min) + 25]$

Definitions: Alb = albumin, AUC = desired area under the curve for carboplatin, BUN = blood urea nitrogen, CrCl = creatinine clearance, GFR = glomerular filtration rate, SCr = serum creatinine.