Estimated glomerular filtration rate (eGFR) and drug dose adjustment using creatinine results with calibration traceable to isotope-dilution mass spectrometry (IDMS).

The major IVD manufacturers have confirmed that all methods, except one, currently on the market are using creatinine reagents and calibrators with calibration traceable to an IDMS reference measurement procedure (1). An exception was the Siemens Dimension Jaffe method which has not been recalibrated. However, in the November 2009 CAP LN24-B Creatinine Accuracy Calibration Verification/Linearity Survey which had values assigned by IDMS at the National Institute for Standards and Technology, the mean and SD results for all methods, including Dimension, met the total error specification for creatinine measurement established by the National Kidney Disease Education Program (NKDEP) (2). Consequently, CAP no longer separates results in the C Survey by the calibration traceability of methods. Over 99% of participants in the C Survey use a method which meets the NKDEP specifications for total error traceable to an IDMS reference measurement procedure.

When calculating eGFR for adults, it is important for laboratories to be sure they are using the correct version of the MDRD equation which has been re-expressed for use with creatinine methods with calibration traceable to IDMS (3) and given below.

\[
eGFR (\text{mL/min/1.73 m}^2) = 175 \times \text{Creatinine}^{-1.154} \times \text{Age}^{-0.203} \times 0.742 \times 1.210 \text{ (If Female) x 1.210 (If African-American)}
\]

An issue of concern to laboratorians, pharmacists and clinical providers is use of eGFR to determine the appropriate dose of drugs for patients with impaired kidney function. Historically, pharmaceutical companies have used estimated creatinine clearance (eCrCl) calculated with the Cockcroft-Gault (CG) equation (4) as the basis for recommendations for drug dose in patients with impaired kidney function. However, there is not a version of the CG equation that is suitable for use with creatinine results with calibration traceable to IDMS. Most creatinine methods had a positive bias relative to IDMS prior to standardized calibration. Consequently, standardized creatinine results are lower than values from older methods and produce a higher eCrCl result with the CG equation.

Examining the drug dose situation using eCrCl prior to standardization of creatinine methods reveals that the variability among creatinine results would have caused variability in eCrCl. Dose recommendations for a particular drug were based on pharmacokinetic data determined with a particular creatinine method. Use of creatinine methods with different calibrations than the one used by the drug manufacturer to develop the drug labeling was a common occurrence and would have caused variability in eCrCl and in the drug dose determined at different health care facilities. For this reason, it is not recommended to attempt to back-calculate from a standardized creatinine result to what might have been expected before standardization and then use that back-calculated value in the CG equation to estimate eCrCl. Using a back-calculated
creatinine value does not address the variability among creatinine methods that existed prior to standardization and which contributed to variability in drug dose determinations.

A large simulation study (5) compared drug dosing recommendations for adults based on eGFR using the MDRD equation and eCrCl using the CG equation, both calculated from standardized creatinine values, to dosing recommendations based on gold-standard measurements of GFR. The results suggested that for the majority of patients and for most drugs tested, there was little difference in the drug dose that would be administered using either equation to estimate kidney function.

Based on these and other considerations, NKDEP’s recommendations (6) are to utilize eGFR or eCrCl for drug dosing. Because the MDRD equation is expressed as adjusted for body surface area, in very large or very small patients, the reported eGFR should be multiplied by the estimated body surface area (BSA) in order to obtain eGFR in units of mL/min which are used in most drug labeling recommendations for dose (see reference 6 for details).

The NKDEP also recommends using a measured GFR (e.g., $^{125}$I-iothalamate) or a measured creatinine clearance (in which case the accuracy of the urine collection is critical) for situations when estimates based on creatinine are likely to be incorrect or for drugs with narrow therapeutic or toxic thresholds which may have adverse consequences.

Conditions when a measured GFR or creatinine clearance should be used:

- Extremes of age and body size
- Severe malnutrition or obesity
- Disease of skeletal muscle
- Paraplegia or quadriplegia
- Evaluation for kidney donation
- Vegetarian diet
- Prior to administration of toxic medications

References


6. For further information see: www nkdep nih gov.

Greg Miller, Ph.D.
Chemistry Resource Committee