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Estimated Glomerular Filtration Rate with and without Race for Drug Dosing: Cystatin C versus Serum Creatinine

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Running Title: Race and Kidney Function in Drug Dosing

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What is already known about this subject:

- Drug dosing adjustment based on estimated kidney function is based on serum creatinine (S_{cr}) with equations that include or exclude race as a covariate.
- Alternate kidney function equations that use serum cystatin C (S_{cys}) do not include race as a covariate but have not been applied for drug dosing.
- Removal of race-based equations in clinical pharmacology is an important element to dismantling structural racism due to the improper attribution of human phenotype to this social construct.

What this study adds:

- Race is not a useful covariate of kidney function for drug clearance estimation.
- Equations that use S_{cys} outperform those that use S_{cr} to estimate the clearance of the model kidney function dependent drug, vancomycin.
- Vancomycin dosing based on non-race-based equations of kidney function are more likely to achieve the probability of target attainment (PTA) than race-based equations.

Abstract

The goal of this study was to use a model kidney function clearance dependent drug (vancomycin) to understand the gain or loss of precision in dosing with use of serum creatinine (S_{cr}), serum cystatin C (S_{cys}), and race and non-race based equations of the estimated glomerular filtration rate (eGFR). In this study of hospitalized patients, we compared S_{cr}, S_{cys}, and their combination to estimate kidney function and vancomycin clearance. The non-race-based S_{cys} eGFR model outperformed other clearance models and improved the probability of target attainment by 15%. When S_{cys} is not available, we show that the new 2021 CKD-EPI $eGFRS_{cr}$ equation (no race factor) performs as well as the current conventional approach. This improvement in model performance does not negate the need for individualized dosing but exemplifies the need to remove race as a factor of kidney-function dose adjustment.

Introduction

Inclusion of race to determine the estimated glomerular filtration rate (eGFR) is controversial.[1] The chronic kidney disease (CKD) epidemiology collaboration (CKD-EPI) eGFR equations using serum creatinine (S_{cr}) and serum cystatin C (S_{cys}) have recently removed the race factor.[2] The United States Food and Drug Administration (US FDA) guidance for industry recommends eGFR or estimated creatinine clearance (eCL_{cr}) to define study inclusion criteria and drug dosing in patients with CKD.[3] The US FDA stipulates that these values be in absolute units (mL/min) and not be body surface area (BSA) indexed (mL/min/1.73 m^2) values.[3] Inaccuracies in kidney function estimates are detrimental to patients with active infections. Reduced therapeutic effect and a higher risk of mortality were seen in stage 3 CKD patients enrolled in phase 3 clinical trials of newer antibiotic agents.[4,5]

Current drug product labels have heterogeneous dosing recommendations based on eCL_{cr} or eGFR with and without BSA indexation.[4,6] Drug dosing models almost exclusively use S_{cr} because of international assay standardization. However, S_{cr} has many limitations, leading to the consideration of serum cystatin C (S_{cys}) as a more predictive endogenous biomarker for eGFR.[7,8] Data comparing S_{cys} to $S_{cr,}$ including their eGFR values as surrogates of drug clearance (CL), are limited but point to an incremental advantage of $S_{cys.}$[9] A direct comparison of these equations is necessary to harmonize drug dosing.[9]

The antibiotic vancomycin is routinely used in practice and serves as an excellent probe drug of the eGFR because over 80% of the dose is eliminated unchanged in the urine.[10] The primary goal of this investigation was to compare S_{cr} to S_{cys} eGFR equations with and without race, and BSA-indexation as predictors of drug CL using vancomycin as the reference

compound. Because significant heterogeneity exists in drug product labels, our secondary goal was to quantify the loss of precision when "lesser" kidney function equations are selected.

Methods

A retrospective study was conducted using patient data from the Michigan Medicine health system. Local institutional review board (IRB) approval was obtained prior to study initiation. Data were obtained from DataDirect, a self-service tool developed by the University of Michigan to collect patient information from the electronic medical record (Epic; Verona, Wisconsin). The study timeframe was October 2010 to August 2020 and patients were included if they were 18 years of age or older; received intravenous vancomycin during an inpatient admission, had serum vancomycin concentration measurements and had both S_{cr} and S_{cys} measurements collected during the same admission. Patients were excluded if there was incomplete vancomycin dosing or concentration information or if they were supported by renal replacement therapy (including hemodialysis and continuous renal replacement therapy). RStudio (RStudio, PBC; Boston, Massachusetts) was used for data manipulation.

The eCL_{cr} was computed using the CG equation with dosing weight (DW); the DW was based on the principle for use of total body weight (TBW) if TBW < ideal body weight (IBW) or adjusted body weight if TBW > 1.25 × IBW, or IBW neither condition is met.[11] The $eGFR_{cr}$ was estimated using the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations.[12,13] The eGFR was also estimated using modified CKD-EPI that incorporated S_{cys} and both S_{cr} and S_{cys}.[14,15] These kidney function estimates were adjusted for body surface area to yield units in mL/minutes.[16]

Pharmacokinetic analyses were performed using Monolix and Sycomore (MonolixSuite 2020R1; Lixoft SAS; Antony, France). For population PK analysis, the stochastic approximation expectation maximization (SAEM) algorithm was used within Monolix 2020R1 and used individual vancomycin dosing and concentration-time data. A one-compartment, zero order input and linear clearance parameterized model was used as the base model and was subsequently modified by testing each demographic and kidney function estimate as a covariate of clearance. This was performed on a stepwise basis by testing each potential covariate independently. The typical values for volume of distribution and CL were estimated using the auto-initiation function in Monolix and matched clinical expectations.

Model discrimination was based on the Akaike Information Criterion (AIC), the goodness of fit plots, and changes to the residual standard error between models. Models were ranked based on the greatest to the smallest change in AIC relative to the base model. For vancomycin dose regimen simulations, Monte Carlo simulations (n = 1,000) were performed with the best performing model and were stratified by eGFR groups (5-14, 15-29, 30-44, 45-59, 60-74, 75-89, 90-119, and 120-180 mL/min). Vancomycin doses of 750 to 1500 mg (250 mg increments) at 8, 12, 24, and 48-hour intervals over a week were simulated and the probability of achieving an AUC_{24} of 400-600 h•mg/L was computed. The typical AUC_{24} in clinical practice is informed after the third or fourth dose. For fair comparisons across eGFR strata, the AUC_{24} at steady state was defined as a value computed between 120-144 hours that allowed for administration of at least three doses in the lowest eGFR group (5-14 mL/min). Longer dosing intervals risk low exposures early in the dosing regimen and so the use of loading doses was also tested. Multiple iterations were tested to identify the optimal pragmatic vancomycin regimen with the 'best'

eGFR model. This dosing nomogram was then tested to compute the PTA for 'lesser' kidney models given that S_{cys} may not be available in some institutions.

Results

Eighty-two patients were included in the analysis with the following values reported as median [5th percentile, 95th percentile]. Fifty percent were male; 81.7% were Caucasian, 54.5 [18, 79] years of age, 69.4 [42.0, 113] kg, and 1.65 [1.40, 1.85] m. The median baseline S_{cr} and S_{cys} values were 1.17 [0.34, 3.19] mg/dL and 2.40 [0.64, 4.02] mg/L, respectively. The patients received a median of three vancomycin doses, and therapeutic drug monitoring included a good distribution of trough measurements (48%) and mid-concentration (random) or peak measurements (52%) (Figure S1).

A one-compartment model provided the optimal structural model fit, and discrimination of covariates of CL through the stepwise model building process is reported here. As shown in Table 1, weight and race did not improve the model relative to age, sex, and height. The inclusion of S_{cys} as a single covariate had the largest reduction in AIC (-81.3 points) compared to S_{cr} (-26.6 points), including eCL_{cr} estimated by the CG equation and S_{cr} based eGFR equations.[2,11-15] Table S1 includes detailed comparisons of ten versions of the CKD-EPI equations using S_{cr}, S_{cys}, and the combination of S_{cr}-S_{cys} in absolute and BSA indexed units with and without race. eGFR translated into absolute units (no BSA) had significantly lower AIC values 8.9 to 17.4 points lower values than BSA-indexed eGFR values (Table S1). For reference, a greater than a 2-point difference in AIC values is considered sufficiently discriminatory of one model over the other. The 2012 CKD-EPI $eGFR_{cys}$ equation demonstrated

the most improvement over the base model with a change in AIC of 97 points (Table S1). Model diagnostics are provided in Figures S1, S2, S3, and S4 to compare the base to the final model (2012 CKD-EPI $eGFR_{cys}$). Using this final model in Monte Carlo simulations, the probability of target attainment for achieving a vancomycin AUC_{24}/MIC (assuming MIC=1 mg/L) of 400 to 600 was 71-74% across pragmatic regimens of eGFR strata (Table 2). Figure S5 illustrates the distributions of simulated concentration-time profiles (n=1000) for this dosing regimen with this final model.

The 2012 CKD-EPI $eGFR_{cys}$ equation does not include a race-based factor and so the next 'best' model based on this analysis if the race is excluded and only S_{cr} is measured, would be the new 2021 CKD-EPI $eGFR_{cr}$ equation (no BSA or race) (Table S1). Using the same eGFR strata the PTA for these vancomycin regimens would be 54-67%. Likewise, using the conventional eCL_{cr} method based on the CG equation is expected to yield a PTA of 58-65% across these regimens (Table 2). Taken together the availability of S_{cys} and use of the 2012 CKD-EPI $eGFR_{cys}$ equation is predicted to improve the PTA by a median [min, max] absolute difference of 15% [4%, 19%] compared to the 2021 CKD-EPI $eGFR_{cr}$ equation.

Discussion

Currently, S_{cr}-based methods of estimating kidney function remain the standard, as reflected in the recent US FDA guidance for establishing dosing recommendations in renal impairment.[16] Increasing evidence supports S_{cys} as a better predictor of kidney function and drug CL compared to S_{cr}. In this analysis, a population pharmacokinetic model that used the CKD-EPI equation and incorporated S_{cys} best-predicted vancomycin CL among a cohort of 82

hospitalized patients. The final $eGFR_{cys}$ model performed better than eCL_{cr}, $eGFR_{cr}$, and $eGFR_{cr\text{-}cys}$ models with and without race as a factor.

This study is not without limitations surrounding generalizability. It is a single-center, retrospective study, which may be biased by uncontrolled confounders or circumstances unique to this institution and patient population. Data collection was narrowed to patients' laboratory values and vancomycin dosing regimens. Information about patients' clinical status, acuity, infection, and outcomes could not be accounted for. While this is a limitation, our results reveal a high likelihood of improvement using S_{cys} compared to S_{cr} in practice. A head-to-head comparison of a S_{cys}-based and S_{cr}-based dosing algorithm for antibiotics such as vancomycin is necessary to confirm our findings. Adopting the use of S_{cys} and 2012 CKD-EPI $eGFR_{cys}$ also reduces the potential for race-based equation bias and may add value to dosing considerations of other agents.[14] The use of the 2021 CKD-EPI $eGFR_{cr}$ equation (no BSA) that excludes race as a factor does not reduce the precision of vancomycin dosing compared to the conventional eCL_{cr} standard if only S_{cr} is available.[2] Extending our findings to other key drugs that require dose adjustment in patients with abnormal kidney function is necessary to support clinical implementation and patient outcomes.

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Table 1. Comparison of pharmacokinetic models with physical characteristics and kidney function biomarkers and estimates tested as a covariate of clearance

Model	AIC	ΔAIC
Base model	1498.6	0
Weight	1501.3	+2.7
Race	1499.6	+1.0
Height	1495.2	-3.4
Sex	1479.9	-18.7
S_{cr}	1472.0	-26.6
Age	1471.1	-27.5
CG (mL min-1)	1464.1	-34.5
MDRD (mL min-1 1.73 m-2)	1464.3	-34.3
MDRD (mL min-1)	1457.4	-41.2
S_{cys}	1417.3	-81.3

S_{cr}: serum creatinine; S_{cys}: serum cystatin C; CG: Cockcroft-Gault; MDRD: Modification of Diet in Renal Disease; AIC: Akaike information criterion; ΔAIC: difference in AIC between covariate model and the base model

Table 2. Probability of target attainment by estimated glomerular filtration rate strata based on pragmatic dose and frequency of administration considerations using three non-race-based equations for estimation of kidney function.

eGFR (mL min-1)	Vancomycin Dosing Regimen	Probability of Target Attainment (PTA) (%)		
		2012 CKD-EPI $eGFR_{cys}$	2021 CKD-EPI $eGFR_{cr}$	1976 CG eCL_{cr}
5-14	1000 mg loading dose, 750 mg every 48 hours	71	67	65
15-29	750 mg every 24 hours	73	66	62
30-44	1000 mg every 24 hours	74	65	58
45-59	1500 mg every 24 hours	73	58	59
60-74	1000 mg every 12 hours	73	55	59
75-89	1250 mg every 12 hours	73	54	58
90-119	1500 mg every 12 hours	72	56	58
120-180	1500 mg every 8 hours	71	56	58

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: estimated glomerular filtration rate (Derivatives incorporating serum creatinine [$eGFR_{cr}$] or cystatin C [$eGFR_{cys}$] were estimated); CG: Cockcroft-Gault; eCL_{cr}: estimated creatinine clearance

The best performing model pharmacokinetic model was used to simulate vancomycin clearance across the spectrum of renal function. The probability of attaining AUC_{24}/MIC 400-600 over a week was estimated.

Supporting information: Refer to Supporting Information for additional tables and figures.