External Validation of Aminoglycoside Models Used in Web Calculators and Clinical Decision Support Systems After Laboratory Conversion to Serum Creatinine Isotope Dilution Mass Spectrometry Assay

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ABSTRACT

Background: Models to predict gentamicin $t_{1/2}$ from serum creatinine (SCr) estimated creatinine clearance (CrCl) are currently being incorporated into smart-device applications and clinical decision support modules without external validation.

Objective: The aim of this study was to determine whether such models remain viable after conversion to isotope dilution mass spectrometry (IDMS) SCr assay.

Methods: This study analyzed data from retrospective reviews of the medical records of nonobese adults receiving the aminoglycoside gentamicin and having ≥2 evaluable serum gentamicin concentrations after laboratory IDMS SCr conversion, from January 2008 to August 2009, at a tertiary care hospital in Florida. A literature search found a number of cited aminoglycoside models. This group of models was classified as group 1. The World Wide Web was also searched for the term *aminoglycoside dosing calculators*, with 6 models found and referred to as group 2. Predictive performance measures were used to compare the model results with the $t_{1/2}$ calculated from gentamicin concentrations using the Nelder-Mead algorithm.

Results: The records of 39 patients met the inclusion criteria (23 men, 16 women; age range, 18–86 years; range of estimated CrCl, 55–115 mL/min) and provided the "gold standard" aminoglycoside $t_{1/2}$. A gentamicin $t_{1/2}$ was predicted from several published models (group 1) and from other models used in online smart-device applications (group 2) and clinical decision modules. The median (interquartile range) root mean square errors were 0.48 (0.44 to 0.65) and 0.48 (0.45 to 0.70) hours from group-1 and -2 models, respectively. The median mean relative prediction errors were 9% (−14% to +13%) and 11% (+1% to +21%) from groups 1 and 2. The median mean absolute prediction errors were 21% (19% to 28%) and 21% (20% to 30%) from groups 1 and 2. Adjusting SCr by +20% improved the predictive ability in 3 of 12 cited models and in 5 of 6 models used in applications.

Conclusions: Models to predict gentamicin $t_{1/2}$ should be externally validated at one's institution before use. The findings from the present study provide a framework for conducting external validation. (*Clin Ther*. 2012;34:803–810) © 2012 Elsevier HS Journals, Inc. All rights reserved.

Key words: Bayes theorem, Bland Altman analysis, clinical decision support modules, computerized physician order entry, elimination rate constant, external validation, gentamicin, half-life, isotope dilution mass spectrometry, nonlinear regression analysis, predictive performance.

INTRODUCTION

Clinicians commonly use 1 of several aminoglycoside models to estimate the initial dose and frequency of conventionally dosed aminoglycoside based on estimated renal function. Despite the widespread use of extended-interval aminoglycoside dosing, there remain patients (eg, those with endocarditis) in whom the extended-interval approach is not suitable or has not been validated. Aminoglycoside models to predict the elimination rate constant (k_e) or clearance (Cl) from estimated creatinine clearance (CrCl) were developed in the 1970s and 1980s. Many years later, the serum creatinine (SCr) assay was recognized as a source of error and inconsistency.

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In 2008, the clinical assay for SCr concentration changed worldwide to the internationally referenced isotope dilution mass spectrometry (IDMS) method.[1] The National Kidney Foundation has led the implementation of this more accurate and standardized calibration for SCr. The new method is more precise, resulting in SCr values that are 0.1 to 0.3 mg/dL lower than before standardization, causing estimates of CrCl to be 5% to 20% higher than before standardization.[2] In the past, some authorities, including the National Cancer Institute, suggested increasing IDMS SCr values by 20% or "back-calculating" to prestandardization values to overcome this discrepancy; however, it is now recognized that no single formula accurately makes this conversion.[3] This assay methodology change and subsequent effect on estimated CrCl implies that aminoglycoside models developed with the formerly used SCr assay methods may no longer be valid.

Despite the potential for inaccuracy arising from the IDMS standardization, these aminoglycoside models are being incorporated into clinical decision support modules that accompany computerized physician order entry in an effort to simplify initial dosing of aminoglycosides.[4] Clinical decision support modules are interactive computer programs (applications, "apps") or other tools designed to assist physicians and other health care professionals with decision making, usually at the point of care.[5] There is an abundance of available web or app-based clinical calculators that may be used in practice to dose aminoglycosides. A brief web search identified thousands of matches for the search term *aminoglycoside dosing calculator*. Several web sites contain functioning calculators that translate patient-specific parameters into dosing regimens. Further investigation into some of the calculators revealed numerous different models that may or may not be referenced. Improper reliance on these calculators to form dosing regimens, without knowledge of the origin of the models or the impact of IDMS SCr values, opens clinicians up to potential error.

The objective of the present study was to assess the ability of the models, 1 group that is cited in the scientific literature and a second group of models from web/app-based programs, to estimate aminoglycoside $t_{½}$ from IDMS SCr–derived CrCl using predictive performance analysis. Additionally, the use of modified SCr (increased by 20%) was evaluated in a before-and-after comparison to determine the effects on the performance of the models. Although the models were developed to predict aminoglycoside k_e, the plasma $t_{½}$ is a better and simpler metric to evaluate, and the 2 parameters are easily interconverted.

MATERIALS AND METHODS

The protocol for this study was considered exempt from review by the institutional review boards at Nova Southeastern University, Ft. Lauderdale, Florida, and the Memorial Regional Hospital, Hollywood, Florida. The IDMS assay method was first used in this institution in August 2007.

Inclusion Criteria and Data Collection

Patients who had received the aminoglycoside gentamicin were identified using records from computerized pharmacy databases. Inclusion criteria were patients aged ≥18 years who had received gentamicin and had ≥2 evaluable gentamicin plasma concentrations available between January 2008 and August 2009.

Patients were excluded based on the following criteria: obesity (defined as actual weight exceeding ideal body weight by ≥1.3-fold), pregnancy, burns, cystic fibrosis, hepatic failure, dialysis therapy, and/or unstable renal function defined by a ≥20% interday variation in SCr over the previous 3 days. Eligible patients also were on no other drugs known to interfere with the aminoglycoside assay.

After enrollment, information pertaining to the pharmacokinetic characteristics of the medication and patients' demographic characteristics were collected, including age, weight, height, diagnosis, drug and dose received, pertinent laboratory values, and plasma gentamicin levels.

Determination of Study Gold Standard Half-life

Each patient had ≥2 evaluable postdistributional plasma gentamicin concentrations, usually representing C_{max} and C_{min}. Aminoglycosides were assayed at the institution using Cobas (Roche Diagnostics, Indianapolis, Indiana).[6] The institution has had pharmacokinetic monitoring available for >30 years; therefore, data collection was routine and accurate. Each patient's gentamicin k_e was calculated by fitting the plasma concentration data to Equation 1 using WinNonLin version 5.3 (Pharsight Corporation, Mountain View, California).[7,8]

$$C = C_0 \cdot e^{-ke \cdot t}, \quad (1)$$

where C_0 and C are the patient's gentamicin concentrations, t is the time of the measurements, and k_e is the