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GFR estimates using cystatin C are superior to serum creatinine in adult patients with cystic fibrosis ☆

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Abstract

Background: Accurate assessment of renal function in patients with cystic fibrosis (CF) is vital for determining the appropriate dose of medications and for early detection of renal disease. Cystatin C (CysC) is a new marker of GFR with reportedly improved accuracy and precision compared to methods incorporating serum creatinine. The purpose of this study is to evaluate the predictive performance of cystatin C in estimating GFR in adult patients with CF.
Methods: Iothalamate was administered to enable measurement of GFR in 38 adult patients with CF and control subjects. Creatinine clearance (C&G) and GFR estimates (cystatin C clearance [Cys C] and abbreviated modified diet in renal disease [aMDRD]) were compared using Bland–Altman and receiver operating characteristic (ROC) analysis. GFR cutoff values of 80 and 90 mL/min–1.73 m^2 were used in the analysis.
Results: The measured GFR was similar in both the CF and healthy volunteers 104 (32.2) and 105 (29.9), $P=0.969$ respectively. No significant difference in mean bias was noted between the predictive methods within the CF population. Cys C provided the most precise estimates of GFR in both populations. ROC curves demonstrated that CysC provided greater sensitivity and specificity compared to the aMDRD (AUC 0.93 vs. 0.54, $P=0.003$) and C&G (AUC 0.93 vs. 0.56, $P=0.005$) in CF at a cutoff GFR of 90 mL/min–1.73 m^2.
Conclusion: Cystatin C clearance provides an improved marker of glomerular filtration rate in CF patients.

Keywords: Glomerular filtration rate; Cystatin C; Creatinine clearance; MDRD

1. Introduction

An accurate assessment of renal function is vital to the dosing and monitoring of drugs and for the early detection of renal disease. This is of particular importance to patients with cystic fibrosis who receive repeated courses of potentially nephrotoxic antibiotics for the treatment of acute pulmonary exacerbations. Two recent reports from the United Kingdom showed that acute renal failure (ARF) associated with intravenous aminoglycosides is increasingly recognized in patients with CF [1,2].

The best index of renal function is glomerular filtration rate (GFR). Iothalamate is considered a gold standard measure for golumerular filtration rate (GFR) assessment, but requires intravenous infusion of the marker compound and timed urine collections over several hours, making this an impractical method for routine clinical use [3].

The most commonly employed methods for quantifying renal function in the clinical setting utilize the endogenous biomarker, serum creatinine, to estimate the patient's glomerular filtration rate. Creatinine is formed as a byproduct of muscle catabolism at a relatively constant rate and is subsequently excreted by the kidney providing a clinically useful marker of

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renal function. However, the use of formulas incorporating serum creatinine is known to result in inaccurate estimations of renal function in patients with malnutrition, liver disease, obesity, or significant third spaced fluid [4]. In addition, certain foods rich in creatine (e.g. red meat) and drugs that affect the tubular excretion of creatinine (e.g. cimetidine) can alter serum creatinine concentrations independent of glomerular filtration [5]. Malnutrition, which occurs as a consequence of pancreatic insufficiency and the increased metabolic needs secondary to impaired respiratory function, is a frequent complication of cystic fibrosis. A reduced muscle mass in patients with CF may account for the overestimation of renal function utilizing methods incorporating serum creatinine noted in a recent report [6].

An alternative endogenous biomarker to estimate GFR is cystatin C, a cysteine proteinase inhibitor involved in the intracellular catabolism of proteins. Structural analysis of the gene and its promoter demonstrate that Cys C is constitutively expressed by all nucleated cells exhibiting a stable production rate even in the presence of an acute inflammatory response [7]. It is freely filtrated in the renal glomeruli and almost completely reabsorbed and catabolized by the proximal tubular cells [8]. Studies performed in patients with various degrees of renal function, liver disease, and spinal cord injuries have shown a higher correlation and improved accuracy in predicting GFR when compared with methods incorporating serum creatinine. [9]. However, results in patients with diabetes, pediatric patients, and those with early renal impairment did not show a significant difference between Cys C and the formulas utilizing creatinine in predicting GFR, indicating the performance may be patient population specific [10–15]. Considering the malnutrition and associated loss of muscle mass often observed in patients with CF an evaluation of utility of cystatin C is warranted. Therefore, the aim of this study was to compare the predictive performance of Cys C clearance relative to existing methods for estimating GFR in patients with CF and age-matched controls.

2. Methods

2.1. Study population and study design

Subjects were selected from two different open label randomized studies evaluating the pharmacokinetics of dicloxacillin and fexofenadine in cystic fibrosis (CF) patients compared to healthy volunteers (HV) [16,17]. During these studies glomerular filtration rate (GFR) was measured using iothalamate as a biomarker. Thirty-eight subjects, 19 cystic fibrosis (CF) patients and 19 age-matched healthy volunteers, were included in the present study. All CF patients had a confirmed diagnosis of cystic fibrosis (positive sweat chloride test and/or known CF genotype). None of the patients were currently pregnant or nursing an infant, post solid organ transplantation, or had significant anemia, renal or hepatic insufficiency. All subjects were older than 18 years and within 70–130% of their ideal body weight. The study protocol was approved by the Institutional Review Board, and each subject signed a written witnessed informed consent prior to participation in the study. After completion of the informed consent each subject participated in a screening visit, which included a review of medical history and physical examination (vitals, height, and weight). Laboratory analysis included a complete metabolic panel and complete blood count. All clinical work in both studies was performed at the General Clinical Research Center (GCRC) at LAC+USC Medical Center.

2.2. Study protocol

Subjects were admitted to the GCRC after an overnight fast. A single dose of iothalamate meglumine 456 mg (Conray 30; Mallinkrodt, St. Louis, MO) was administrated as an intravenous push dose 1 h after an oral fluid load of 600 ml of caffeine-free, sugar-free liquids. An oral fluid regimen was maintained at 150–200 ml/h for 6 h following the drug administration to ensure sufficient hydration during the urine collection period. Blood samples were drawn at times 0, 0.25, 0.5, 1, 2, and 3 h after dosing for all subjects in both studies. Samples were kept on ice until plasma was separated by centrifugation within 30 min of collection. Urine samples were obtained from spontaneous voiding every 30 min for the first 3 h after iothalamate administration. Both urine and plasma samples were stored at −70 °C until the time of analysis.

2.3. Determination of plasma and urinary iothalamate concentrations

Iothalamate urine and plasma samples were analyzed based on a previously published method [18]. Standard curves were created by linear regression of peak area ratio of iothalamate to theophylline (internal standard) versus known concentrations of iothalamate. The plasma and urine standard curves were linear in the range from 2–60 μg/ml and 10–250 μg/ml with correlation coefficients of at least 0.99 and 0.98 respectively in the first study and 0.94 and 0.99 respectively in the other. Unknown samples were estimated by applying the equation of the linear regression of the standard curve to the unknown sample peak area. The inter-day coefficients of variation (CV) for plasma and urine samples were less than 11% in both studies.

2.4. Pharmacokinetic analysis

Pharmacokinetic analysis was performed by applying a 1-compartment model with first order elimination to the measured plasma and urinary concentrations of iothalamate using the ADAPT II software (release 5, Biomedical Simulations Resource, University of Southern California, Los Angeles). Analysis was performed using the parametric expectation maximization algorithm. The dose, plasma and urine iothalamate concentrations, and the urine volumes were the inputs to the model. Iothalamate clearance was modeled with renal and nonrenal clearances. The primary output parameter of interest was the renal clearance, which was used as the measured GFR for each subject.

2.5. Data analysis

Creatinine clearance was estimated using the method of Cockcroft–Gault and normalized for body surface area. Measured GFR