The Impact of Different Renal Function Measuring Methods on the Dosages of Meropenem, Piperacillin/Tazobactam and Cefepime in Critically Ill Patients

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Abstract

Objective: Assessment of dosage deviations of 3 β-lactam antibiotics eliminated through the kidneys (meropenem, piperacillin/tazobactam, and cefepime) by comparison of 2 prediction formulae, Cockroft-Gault (CG) and Modification of Diet in Renal Disease (MDRD) with 24 h urinary creatinine clearance ($CrCl_{24h}$), as a reference method.

Method: 125 samples of 61 critically ill patients (each one with CG, MDRD and $CrCl_{24h}$ values) were classified in one of the 5 stages of the National Kidney Foundation (NKF) according to $CrCl_{24h}$. Dosage discrepancies for each antibiotic based on CG and MDRD were studied in reference to $CrCl_{24h}$ by percentage agreement and weighted kappa. At each of the NKF stages, daily dosage differences (Δ=DoseCG-Dose$CrCl_{24h}$; Δ=DoseMDRD-Dose$CrCl_{24h}$) and percentage of samples with dosage discrepancies by CG and MDRD in reference to $CrCl_{24h}$ were calculated.

Results: There were no statistically significant differences between the 2 prediction formulae in respect to $CrCl_{24h}$, achieving good degrees of concordance. Deviation percentages fluctuated between 15.2% and 28% and occurred mainly by underdosing on stages 1 and 2 and by overdosing on stages 4 and 5.

Conclusions: The 2 renal function prediction formulae can be indistinctly used to optimize the β-lactam antibiotics dose regimen, CG being the easiest one.

Key words: β-lactam antibiotics. Glomerular filtration. Cockcroft-Gault. MDRD. Critically ill patients.

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Impacto de distintos métodos de estimación de la función renal en la dosificación de meropenem, piperacilina/tazobactam y cefepima en pacientes críticos

Objetivo: Evaluar las desviaciones de dosificación de 3 antibióticos betalactámicos eliminados por vía renal (meropenem, piperacilina/ tazobactam y cefepima) mediante la comparación de 2 fórmulas de predicción de función renal, Cockroft-Gault (CG) y Modification of Diet in Renal Disease (MDRD), con el aclaramiento de creatinina en orina de 24 h ($ClCr_{24h}$) como método de referencia.

Método: Las 125 muestras de 61 pacientes (cada una con sus valores de CG, MDRD y $ClCr_{24h}$) de una unidad de cuidados intensivos (UCI) se clasificaron en los 5 estadios definidos por la National Kidney Foundation (NKF) en función del $ClCr_{24h}$. Se estudiaron las discrepancias de dosificación de cada antibiótico según CG o MDRD en referencia al $ClCr_{24h}$ por acuerdo porcentual e índice kappa ponderado. En cada estadio de NKF se cuantificaron las diferencias de dosificación diaria (Δ = DosisCG-Dosis$ClCr_{24h}$; Δ = DosisMDRD-Dosis$ClCr_{24h}$) y el porcentaje de muestras con discrepancias de dosificación por CG y MDRD en referencia al $ClCr_{24h}$.

Resultados: En ningún caso se observaron diferencias estadísticamente significativas entre ambas fórmulas con respecto al $ClCr_{24h}$, obteniendo grados de concordancia buenos. Los porcentajes de desviaciones oscilaron del 15,2% al 28% y ocurrieron mayoritariamente por infradosificación en los estadios 1 y 2, y por sobredosificación en los estadios 4 y 5.

Conclusiones: Las dos predicciones de función renal en pacientes de la UCI pueden ser empleadas indistintamente para la dosificación de betalactámicos, aunque la de CG es la más sencilla.

Palabras clave: Antibióticos betalactámicos. Filtrado glomerular. Cockcroft-Gault. MDRD. Pacientes críticos.

INTRODUCTION

Glomerular filtration rate (GFR) is measured as the urinary clearance of an ideal filtration marker such as inulin, ^{125}I-iothalamate, ^{51}Cr-EDTA (^{51}Cr-ethylene diamine tetraacetic acid), ^{99m}Tc-diethylene-triamine-penta-acetic acid, or iohexol. The basic quality of an ideal marker is it almost totally filtrating in its passing through the renal glomerulus, without experiencing subsequent tubular processes of reabsorption and secretion. However, in clinical practice, exogenous filtration markers are hardly used given their high cost, the work involved, complex measurement, and in some, radioactivity.[1,2] In the case of a required exact measurement of a glomerular filtration value, the use of iohexol as a contrast agent is highly recommended, considering it is relatively inexpensive, non-radioactive, has a very good correlation with glomerular filtration rate values obtained with inulin,[3,4] insurance for special populations of patients, including those with serious renal insufficiency,[4] and it is relatively simple, considering that urinary samples are not required.[5] Furthermore, in patients with a GFR >40 mL/min · 1.73 m^2 only a plasma sample is required a few hours after its administration[5] which, compared with inulin, means saving cost and time derived from the need for a bolus and infusion until reaching a state of stable equilibrium, and obtaining blood and urine collections.[6] As an alternative to exogenous markers, the quantification of an endogenous filtration marker was prescribed, which is 24 h urinary creatinine, coming from catabolism of muscular creatine, or hepatic, in low proportion. Even though it is the most widely used reference method in clinical treatment, it is a suboptimal marker[7] due to some limitations, considering that its production is inconstant, and its analytical quantification is not without difficulties. Creatinine production varies according to age, sex, race, pregnancy, nutritional state, diet, muscular mass and muscular diseases, immobilization, diabetes mellitus, and some medicines (increase of serum creatinine due to inhibition of tubular secretion from cimetidine, probenecid or trimethoprim, and nephrotoxic drugs), among others. Analytical quantification is influenced by the obtainment process, laboratory techniques (analytical interferences of reagents with physiological substances, etc), and physiopathologic situations (dehydration, edemas, cirrhosis, cardiovascular disease, cancer, diabetes, use of vasoactive, and diuretic substances), which significantly affect the resulting value of 24 h urinary creatinine clearance ($CrCl_{24h}$) and, consequently, the estimation of actual glomerular filtration rate (aGFR).[1,8] This presents complications in unstable patients in intensive care units (ICU)[9,10] because of the high variability inherent in these situations related to morbidity, perfusion of diuretic and vasoactive substances,[9] and hemodynamic and renal instability throughout the 24 h of urine collection[9,10] (correct measurement of $CrCl_{24h}$ requires stable renal function).[11]

In an attempt to resolve the mentioned problems, it has been proposed that urinary clearance collected in 2 h ($CrCl_{2h}$) compared with $CrCl_{24h}$ be measured in ICU patients, but with the scarcity of studies, this is still not generalizable.[9] Other authors decided upon 1 ($CrCl_{1h}$)[10] in place of $CrCl_{24h}$ as a reference for the evaluation of predictors of glomerular filtration. Considering the complexity and limitations of quantification of 24 h urinary creatinine, and with the purpose of simplifying it regarding assistance, various formulas of glomerular filtration estimation were proposed based on serum creatinine, of which the most used in dosage of medicines are, first, Cockcroft-Gault (CG), and secondly, Levey or Modification of Diet in Renal Disease (MDRD).[1,12] Creatinine clearance (CrCl) supposes a systematic overestimation of 10% or 20% of the GFR, due to the fact that creatinine goes through a tubular secretion process, a reason why some researchers proposed a correction of this bias through the product GFR = 0.84 · CrCl.[13] Regardless of this, creatinine clearance values and GFR are interchangeable[2] in clinical practice.

There is another endogenous marker of glomerular filtration, similar to serum cystatin-C, which appears to be more precise in quantification of glomerular filtration, even though an improvement regarding equations of estimation of glomerular filtration based on the serum creatinine value has still not been demonstrated with adequate certainty,[1] and it has not been validated in special populations.[2,14,15]

The importance of evaluation of renal function in critically ill patients for a correct individualization of pharmacotherapeutic regimens is unquestionable.[16] In a recent study, with a main objective of comparing critically ill ICU patients with 2 formulas for estimating creatinine clearance as a marker of glomerular filtration, *a)* Cockcroft-Gault (CG), and *b)* MDRD, using 24 h urinary creatinine clearance values ($CrCl_{24h}$) as a reference, expressed in mL/min, no significant differences were observed among them.[17] In the study, it was concluded that either of the formulas could be used in this population of patients. However, an individualized data analysis demonstrated that in some patients notable differences were observed between creatinine clearance values obtained by the reference method ($ClCr_{24h}$) and values of estimated GFR (eGFR) for each one of the 2 formulas, CG and MDRD.

The objective of this study is to analyze possible clinical consequences regarding of the dosage of antibiotic medicines such as cefepime, piperacillin/tazobactam, and meropenem, which are principally eliminated through the kidneys.

METHOD

Patients

Observational and retrospective study carried out on adult patients admitted into various ICU's of a university hospital with 800 beds. In the study, 125 samples from 61 patients were included during a period of 2 years, and those who received extracorporeal purification techniques (hemodialysis, hemofiltration, etc) were excluded.