Evaluating the usefulness of the estimated glomerular filtration rate for determination of imipenem dosage in critically ill patients

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Background. Antibiotic dosing in critically ill patients is complicated by variations in the pharmacokinetics of antibiotics in this group. The dosing of imipenem/cilastatin is usually determined by severity of illness and renal function.
Objectives. To determine the correlation between estimated glomerular filtration rates (eGFRs) calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and imipenem trough levels in critically ill patients.
Methods. This prospective observational study was done in the surgical intensive care unit (ICU) at Steve Biko Academic Hospital, Pretoria, South Africa. Imipenem trough levels were measured by high-performance liquid chromatography and compared with eGFRs calculated with the CKD-EPI equation. Correlation was evaluated by the Pearson product-moment correlation coefficient.
Results. The study population consisted of 68 critically ill patients aged between 18 and 81 years; 43 (63%) were male, and the mean weight was 78 kg (range 40 - 140). On admission, 30 patients (44%) had sepsis, 16 (24%) were admitted for trauma, and 22 (32%) were admitted for miscellaneous surgical conditions. Acute Physiology and Chronic Health Evaluation II (APACHE II) scores ranged from 4 to 39 (mean 18). The 28-day mortality rate was 29%. The mean albumin level was 16 g/L (range 7 - 25), the mean creatinine level 142 µmol/L (range 33 - 840), and the mean eGFR 91 mL/min/1.73 m^2 (range 6 - 180). Imipenem trough levels ranged between 3.6 and 92.2 mg/L (mean 11.5). The unadjusted Pearson product-moment correlation coefficient between eGFR and imipenem trough level was –0.04 (p=0.761).
Conclusion. Considering the high mortality rate of sepsis in ICUs and the rapid global increase in antimicrobial resistance, it is crucial to dose antibiotics appropriately. Owing to the variability of antibiotic pharmacokinetics in critically ill patients, this task becomes almost impossible when relying on conventional dosing guidelines. This study found that eGFRs do not correlate with imipenem blood levels in critically ill patients and should not be used to determine the dose of imipenem/cilastatin. Instead, the dose should be individualised for patients through routine therapeutic drug monitoring.

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Bacterial infections are major contributors to morbidity, mortality and healthcare costs in intensive care units (ICUs).[1] Without appropriate treatment, sepsis and septic shock are rapidly fatal.[2] It is therefore crucial to dose antibiotics correctly, especially in critically ill patients.[3] Incorrect dosing of antibiotics in critically ill patients may result in increased morbidity and mortality, and the development of multidrug-resistant organisms.[4] Antibiotic dosing in critically ill patients is complicated by differences in the pharmacokinetics of antibiotics between critically ill patients and healthy persons.[5,6] The most important causes of these differences are related to capillary leak syndrome, end-organ dysfunction, augmented renal clearance and hypoalbuminaemia.[7,8] Imipenem/cilastatin is a combination of a broad-spectrum beta-lactam antibiotic and a dehydropeptidate-1 inhibitor.[9] It is necessary to combine imipenem with cilastatin to prevent the rapid degradation of imipenem by the enzyme dehydropeptidase-1 in the kidneys.[10] Imipenem/cilastatin is widely used to treat infections in critically ill patients in ICUs.[11] The antibacterial effect of imipenem is determined by the percentage of time within the dosing interval spent above the minimum inhibitory concentration (fT>MIC).[12] The dosing regimen, specifically in special population groups such as critically ill patients, is therefore determined by the pharmacokinetic properties of imipenem.[13] The pharmacokinetic-pharmacodynamic target of imipenem in critically ill patients recommended by recent reports is 100% fT>MIC.[14,15] Imipenem therapeutic drug monitoring is not widely available outside Europe and Australia.[15,16] The dosing of imipenem is usually determined by standard dosage guidelines that consider the severity of illness and creatinine clearance.[17-19] These guidelines were derived from pharmacokinetic studies done in healthy volunteers.[20,21] The dosage range for adults with normal renal function and body weight ≥70 kg recommended in the package insert is between 250 and 1 000 mg every 6 - 12 hours.[18] In the absence of therapeutic drug monitoring, the main determinant of imipenem/cilastatin dosage in critically ill patients is creatinine clearance (CrCl). However,

since most clinical laboratories report the estimated glomerular filtration rate (eGFR) and not CrCl, it is likely that the eGFR is commonly used for drug dosage adjustments.[22-24] Measuring urinary CrCL is cumbersome and prone to errors, and owing to the time required for urine collection, results are delayed compared with eGFR.[24] Although CrCl is the most common method of estimating renal function for drug dosing, the availability and clinical use of the eGFR provides clinicians with an alternative.[25,26] Ideally, the clinician should have information on the absolute renal function, obtained by measuring CrCl, to correctly dose drugs. However, reports have shown that a relative measure of GFR may also be used to sensibly adjust dosing.[22,25-27] If a drug is solely renally eliminated, its clearance is equal to the GFR.[27] Previous studies have shown that reliance on conventional dosage guidelines as described above may not achieve therapeutic targets in critically ill patients.[17,28-31] A recent position paper on antimicrobial therapeutic drug monitoring in critically ill adult patients authored by an expert panel on behalf of the Infection Section of the European Society of Intensive Care Medicine, the Pharmacokinetic/Pharmacodynamic and Critically Ill Patient study groups of the European Society of Clinical Microbiology and Infectious Diseases, the Infectious Diseases Group of the International Association of Therapeutic Drug Monitoring and Clinical Toxicology, and the Infections in the ICU and Sepsis Working Group of the International Society of Antimicrobial Chemotherapy recommended that therapeutic drug monitoring be routinely performed when beta-lactam antibiotics are used in critically ill patients.[15] Despite this recommendation, the routine use of therapeutic drug monitoring of beta-lactam antibiotics has not been widely adopted.

The objective of this study was to determine the correlation between eGFR and imipenem trough levels of critically ill patients admitted to the surgical ICU of Steve Biko Academic Hospital, Pretoria, South Africa.

Methods

This prospective observational study was approved by the Faculty of Health Sciences Research Ethics Committee of the University of Pretoria (ref. no. 473/2017). Patients were recruited from the surgical ICU at Steve Biko Academic Hospital between March 2018 and October 2019. Informed written consent was obtained from each patient or from the patient's next of kin if the patient was incapacitated. The eligibility criteria were as follows: ≥18 years of age, admission to the surgical ICU, and imipenem/cilastatin therapy (prescribed at the discretion of the treating clinician). Patients received imipenem/cilastatin doses ranging from 500 to 1 000 mg, infused over 3 hours, every 6 - 12 hours. The dose was determined based on the eGFR as follows: patients with an eGFR >70 mL/min/1.73 m^2 received 1 000 mg 6-hourly, those with an eGFR between 41 and 70 mL/min/1.73 m^2 received 750 mg 8-hourly, those with an eGFR between 21 and 40 mL/min/1.73 m^2 received 500 mg 8-hourly, and those with an eGFR <21 mL/min/1.73 m^2 received 500 mg 12-hourly. The eGFR was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[32] Exclusion criteria included any patient who withheld consent or who did not fulfil all of the eligibility criteria. Clinical and demographic information, including the Acute Physiology and Chronic Evaluation II (APACHE II) score,[33] was collected from hospital files. Trough blood samples were collected in heparinised collection tubes (Beckton, Dickinson and Company, USA) from each patient, prior to re-dosing, after at least four doses of imipenem/cilastatin had been administered. This was done to approximate steady-state imipenem levels.[14] Immediately after collection, the samples were transported to the microbiology laboratory and centrifuged at 5 000 revolutions per minute for 10 minutes to separate the plasma. Two millilitres of plasma were then removed and added to two millilitres of an ethylene glycol and 2-N-morpholine-ethane sulfonic acid solution (1:1) (Sigma-Aldrich, USA) and stored at –70°C until analysis. High-performance liquid chromatography (HPLC) was utilised to measure the imipenem levels in the specimens. The details of the method used have been published previously.[34] HPLC was performed on a Shimadzu Ultra Fast Liquid Chromatography system (Shimadzu Corp., Japan). Analytical-grade imipenem that was used in the analysis was obtained from the European Directorate for the Quality of Medicines & HealthCare (Strasbourg, France). Stata release 15 software (StataCorp, USA) was used for the statistical analysis. Correlation between the eGFR and imipenem trough plasma levels was evaluated by the Pearson product-moment correlation coefficient.

Results

The study recruited patients during the period 1 March 2018 - 31 October 2019. During this period, 69 patients were eligible for recruitment. Of these, 68 patients provided informed consent and were included in the analysis. One patient withheld consent and was excluded from the study. The study population consisted of 43 males (63%), the mean age was 47 years (range 18 - 81), and the mean weight was 78 kg (range 40 - 140). On admission, 30 patients (44%) had sepsis, 16 (24%) were admitted for trauma, and 22 (32%) were admitted for miscellaneous surgical conditions. The APACHE II scores ranged from 4 to 39 (mean 18). The mean length of ICU stay was 16 days. The 28-day mortality rate was 29%. In terms of comorbid conditions, 25 patients (37%) had cardiovascular disease, 13 (19%) had renal disease, 11 (16%) had HIV infection, 9 (13%) had diabetes mellitus, 8 (12%) had malignancy, 5 (7%) had respiratory disease and 4 (6%) had tuberculosis. Most infections (n=57; 84%) were hospital acquired. The most common sites of infections were bloodstream (n=42), intra-abdominal (n=35), lower respiratory tract (n=16), skin and soft tissue (n=12), genitourinary tract (n=7), line sepsis (n=7) and surgical site (n=4). Infections at more than one site occurred in 42 of the patients (62%). The mean albumin level was 16 g/L (range 7 - 25), the mean creatinine level 142 µmol/L (range 33 - 840) and the mean eGFR 91 mL/min/1.73 m^2 (range 6 - 180). The eGFR was <60 mL/min/1.73 m^2 in 24 patients (35%) and >130 mL/min/1.73 m^2 in 20 (29%). Imipenem trough levels ranged from 3.6 to 92.2 mg/L (mean 11.5). The unadjusted Pearson product-moment correlation coefficient between the eGFR and the imipenem trough level was –0.04 (p=0.761). After excluding the two highest imipenem trough plasma levels (44.9 mg/L and 92.2 mg/L) as outliers, the correlation was –0.22 (p=0.077). The relationship is illustrated by scatter plots in Figs 1 and 2.

Discussion

Mortality rates from sepsis in ICUs range from 28% to 76%.[1] In the present study, the 28-day all-cause mortality rate was 29%. In the Defining Antibiotic Levels in Intensive Care Unit Patients (DALI) study, 16% of patients were found to have subtherapeutic beta-lactam levels.[3] These patients were 32% less likely to have a positive clinical outcome compared with those with therapeutic beta-lactam levels.[3] Several studies done in critically ill patients have found evidence of variable and low antibiotic concentrations when conventional dosing regimens are used.[35-37] Augmented renal clearance is a well-known reason for subtherapeutic levels of drugs with renal elimination.[8,36] Increased cardiac output results in increased blood flow through the kidneys and a subsequent increase in glomerular filtration rate that leads to increased elimination of drugs.[8,29] In the present study,

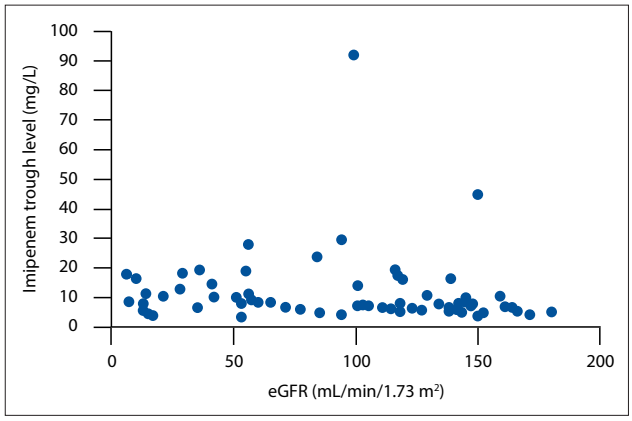

Fig. 1. Scatter plot illustrating the correlation between eGFR and imipenem trough levels. (eGFR = estimated glomerular filtration rate.)

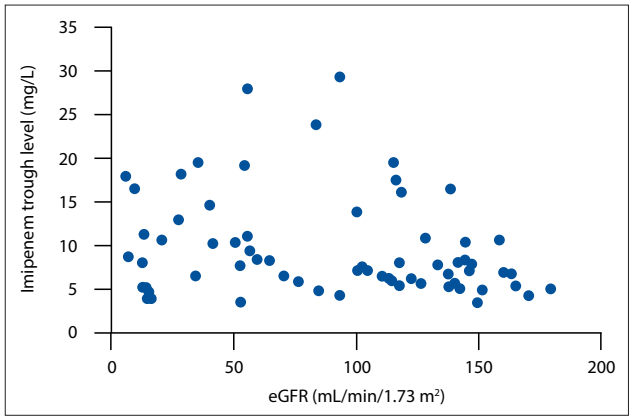

Fig. 2. Scatter plot illustrating the correlation between eGFR and imipenem trough levels. Note that the two highest imipenem trough levels were excluded from this figure to better illustrate the data dispersion. (eGFR = estimated glomerular filtration rate.)

20 (29%) of the patients had eGFR levels >130 mL/min/1.73 m^2. Pharmacokinetic studies of imipenem in critically ill patients report subtherapeutic imipenem levels in up to 70% (range 0 - 70%) of ICU patients.[17,28-31] These findings suggest that conventional imipenem dosage guidelines depending on CrCl may be unreliable. Since imipenem is primarily excreted renally and has a short half-life, a significant correlation between imipenem levels and renal function is expected.[9,38] However, previous pharmacokinetic studies on imipenem in critically ill patients have reported mixed results on this relationship, with some reporting significant correlation and others not.[13,17,19,38,39] In the present study, we expected to find a linear inverse relationship between eGFR and imipenem trough levels, since imipenem is principally renally excreted and the dosage of imipenem was determined by the eGFR. Interestingly, we found a poor correlation between the two variables that is clearly illustrated by Figs 1 and 2 and supports the findings and conclusions of previous reports that imipenem levels are not predictable in critically ill patients.[17,34,40,41] The result suggests that there are other factors influencing trough imipenem plasma concentrations. The implication of this finding is that one cannot simply adjust the dose of imipenem/cilastatin based on the eGFR in critically ill patients. To measure the adequacy of imipenem/cilastatin dosing in terms of antibacterial activity and to support dose optimisation, therapeutic drug monitoring is a powerful tool, especially in special population groups such as critically ill patients.[15] The extensive pharmacokinetic variability of imipenem in critically ill patients renders conventional dosing strategies obsolete. Therapeutic drug monitoring guided dosing offers a safe and effective way to ensure that optimal antimicrobial exposure is achieved in all critically ill patients. Unfortunately, therapeutic drug monitoring of beta-lactam antibiotics is not widely available in SA. The growing magnitude of the antimicrobial resistance burden certainly serves as an impetus for the implementation of therapeutic drug monitoring of beta-lactam antibiotics in routine clinical practice. To demonstrate the return on investment of such a strategy, well-designed randomised clinical trials are necessary.

Study limitations

This study has important limitations that should be considered. As it was conducted at a single centre and has a small sample size, the results may not be globally applicable. As it was a non-interventional study, we only analysed a single plasma sample from each patient. The findings therefore do not adequately represent the variability of imipenem plasma levels in critically ill patients during the treatment interval.

Conclusion

Considering the high mortality rate of sepsis in ICUs and the rapid global increase in antimicrobial resistance, it is crucial to dose antibiotics appropriately. The variability of antibiotic pharmacokinetics in critically ill patients renders this task almost impossible with sole reliance on conventional dosing guidelines. We found that eGFRs do not correlate with imipenem blood levels in critically ill patients. The implication of this finding is that the eGFR should not be used to determine the dose of imipenem/cilastatin in this population. Instead, the dose should be individualised for patients through routine therapeutic drug monitoring.

Declaration. None.

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Conflicts of interest. None.

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