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Augmented renal clearance, low β-lactam concentrations and clinical outcomes in the critically ill: An observational prospective cohort study

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ABSTRACT

Whilst augmented renal clearance (ARC) is associated with reduced β-lactam plasma concentrations, its impact on clinical outcomes is unclear. This single-centre prospective, observational, cohort study included non-pregnant, critically ill patients aged 18–60 years with presumed severe infection treated with imipenem, meropenem, piperacillin/tazobactam or cefepime and with creatinine clearance (CL_{Cr}) ≥60 mL/min. Peak, intermediate and trough levels of β-lactams were drawn on Days 1–3 and 5. Concentrations were deemed 'subthreshold' if they did not meet EUCAST-defined non-species-related breakpoints. Primary and secondary endpoints were clinical response 28 days after inclusion, and ARC prevalence (CL_{Cr} ≥ 130 mL/min) and subthreshold and undetectable concentrations, respectively. Logistic regression was used to evaluate associations between ARC, antibiotic concentrations and clinical failure. From 2010 to 2013, 100 patients were enrolled (mean age, 45 years; median CL_{Cr} at inclusion, 144.1 mL/min). ARC was present in 64 (64%) of the patients. Most patients received imipenem/cilastatin (54%). Moreover, 86% and 27% of patients had at least one subthreshold or undetectable trough level, respectively. Among imipenem and piperacillin trough levels, 77% and 61% were subthreshold, respectively, but intermediate levels of both antibiotics were largely above threshold. ARC strongly predicted undetectable trough concentrations (OR = 3.3, 95% CI 1.11–9.94). A link between ARC and clinical failure (18/98; 18%) was not observed. ARC and subthreshold β-lactam antibiotic concentrations were widespread but were not associated with clinical failure. Larger studies are necessary to determine whether standard dosing regimens in the presence of ARC impact negatively on clinical outcome and antibiotic resistance.

1. Introduction

β-Lactam antibiotics exhibit time-dependent bacterial killing [1]. Because most β-lactam antibiotics have little or no post-antibiotic effect on most organisms [2], optimal antimicrobial efficacy is achieved when the antibiotic's plasma concentration remains above the minimum inhibitory concentration (MIC) of the targeted organism(s) throughout the dosing interval ($T > MIC_{100\%}$) [2].

Most β-lactam antibiotics are renally cleared; pharmacokinetic studies document an inverse relationship between creatinine clearance (CL_{Cr}) and β-lactam trough concentrations [3,4]. According to current practice, however, a patient with a CL_{Cr} of 60 mL/min will typically receive the same dosing as a patient with a CL_{Cr} two or even three times higher. Augmented renal clearance (ARC) refers to enhanced renal elimination of circulating solute and is generally defined as $CL_{Cr} \geq 130$ mL/min/1.73 m^2 [5]; it is described with increasing frequency in the critically ill, particularly in their initial

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and most acute phase of illness [6]. At present, ARC eludes strict definition: it may arise not only as a result of glomerular hyperfiltration, but also through increased renal tubular secretion and/or decreased reabsorption [6].

Critically ill patients with ARC have an increased risk for low β-lactam antibiotic plasma concentrations. Udy et al. recently examined the CL_{Cr} and β-lactam trough concentrations of 58 intensive care unit (ICU) patients: CL_{Cr} values ≥130 mL/min/1.73 m^2 were associated with trough concentrations less than the MIC of the antibiotic needed to inhibit the targeted micro-organism in 82% of patients [5].

Existing literature on ARC and subtherapeutic drug concentrations remains largely pharmacokinetic, however. Studies specifically examining clinical outcomes in patients with ARC and potentially subtherapeutic β-lactam antibiotic concentrations are lacking. We therefore designed a prospective cohort study to explore the links, if any, between ARC, plasma concentrations of four frequently used β-lactam antibiotics, and clinical outcome in the critically ill.

2. Materials and methods

2.1. Study setting and population

This prospective observational cohort study was conducted from May 2010 through October 2010 and from July 2011 through May 2013 at the 34-bed mixed medical and surgical ICU of the Geneva University Hospitals (HUG) (Geneva, Switzerland), which admits over 2500 critically ill patients per year with a mean length of stay of 4 days. The temporary cessation of recruitment was related to the departure of study personnel.

In May 2013, a convenience sample of adult patients was included: they were aged 18–60 years, required intensive care and were diagnosed with suspected or documented severe bacterial infections for which antibiotic therapy with intravenous imipenem/cilastatin, meropenem, piperacillin/tazobactam or cefepime had recently been initiated. The usual dosing regimens at HUG for these antibiotics in the ICU are 500 mg four times daily, 2 g three times daily, 4.5 g three times daily and 2 g twice daily, respectively [7–9]. Meropenem is given at the higher dose because it is commonly used in place of imipenem for severe cerebral infections.

Patients who were pregnant, had a calculated CL_{Cr} < 60 mL/min, with a body mass index (BMI) <18 kg/m^2 or >30 kg/m^2 or had already received the study antibiotic for >2 days were excluded. Patients receiving combination therapy with additional antibiotics were not excluded. The University Hospital's Ethics Committee approved the study and, given its observational nature, waived the requirement for informed consent from patients who were unconscious or otherwise unable to understand the study protocol.

2.2. Study procedures

Patients were included on their first or second day of β-lactam antibiotic therapy (Day 0 or 1, respectively). CL_{Cr} was monitored at inclusion and on Days 1–7, 14 and 28. Therapeutic drug monitoring (TDM) included peak (C_{max}), intermediate (midway between two consecutive β-lactam antibiotic administrations, $T_{40–60\%}$) and trough concentrations ($T_{100\%}$) collected on Days 1, 2, 3 and 5 of therapy. For patients receiving piperacillin/tazobactam or imipenem/cilastatin, only the active β-lactam component was monitored. The patient's clinical course was followed through Day 28.

2.3. Definitions

The key inclusion criterion was clinically suspected or microbiologically proven severe bacterial infection of all types, including clinical sepsis (even in the absence of a proven focus of infection). Microbiological evidence proving infection was defined as positive cultures of blood, cerebrospinal fluid or tissue, urine, intra-abdominal fluid or tissue, deep wound specimens, and bronchoalveolar lavage fluid or high-quality tracheal aspirate, respectively.

CL_{Cr} was estimated at inclusion and on Days 1–7, 14 and 28 (or last follow-up) using the Cockcroft–Gault formula [10]. Direct urinary creatinine measurement was not done. ARC was defined as CL_{Cr} ≥ 130 mL/min.

2.4. Clinical pharmacology and therapeutic drug monitoring targets

The four antibiotics monitored in this study are generally hydrophilic molecules with small distribution volumes. They are renally cleared with little plasma protein binding (8.7%, 8.0%, 16–21% and 16% for imipenem/cilastatin, meropenem, piperacillin/tazobactam and cefepime, respectively) [11–13] and are characterised by a relatively short elimination half-life (1 h in the case of imipenem, meropenem and piperacillin and 2 h in the case of cefepime) [11–13].

Whilst a pharmacokinetic target of $T > MIC_{100\%}$ was desired [2,14], this pilot study did not allow for routine individual MIC testing on all isolated micro-organisms, reflecting current clinical practice in most ICUs. Thus, intermediate and trough concentrations were measured and were compared with the non-species-related breakpoints published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) from 2010 through 2013: imipenem and meropenem [sensitive (S) ≤ 2 mg/L; resistant (R) > 8 mg/L]; piperacillin/tazobactam (S ≤ 4 mg/L; R > 16 mg/L); and cefepime (S ≤ 4 mg/L; R > 8 mg/L) [15]. β-Lactam concentrations lower than or equal to the susceptible breakpoint were considered potentially subtherapeutic.

2.5. Outcome measures

The primary outcome was clinical response 28 days after inclusion. Clinical cure was defined as complete resolution of all signs and symptoms related to the infection without recurrence; clinical improvement consisted of a marked or moderate reduction in the severity and/or number of signs and symptoms of infection. Clinical failure was defined as insufficient lessening of the signs and symptoms to qualify for improvement, including death or indeterminate [16]. A study physician (AH) evaluated clinical outcomes by means of a prospectively designed classifying system, which used objective signs and biomarkers such as core temperature, C-reactive protein and procalcitonin, as well as data from physicians' and nurses' progress notes.

Secondary outcomes included the prevalence of ARC at inclusion, the duration of ARC, the prevalence of subthreshold and undetectable β-lactam plasma intermediate and trough concentrations, and 28-day all-cause mortality.

2.6. Sampling and β-lactam concentration assay

To ensure that all samples were obtained at steady state, blood was collected for plasma concentration monitoring of imipenem, meropenem, piperacillin and cefepime on the second day of the antibiotic's administration (Day 1) at peak (15–30 min after the end of initial infusion), intermediate (midway between two sequential administrations of the antibiotic, ±30 min) and trough (within

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