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Beta-lactam carryover in arterial and central venous catheters is negligible

Emily Marsh[a], Sylvia M. Verhoven[a], Joseph J. Groszek[a], William H. Fissell[a,*], Guohua An[b], Pratish Patel[c], Buddy Creech[d], Matthew Shotwell[e]

[a] Division of Nephrology and Hypertension, Vanderbilt University Medical Center, Nashville, TN, United States of America
[b] Division of Pharmaceutics and Translational Therapeutics College of Pharmacy, University of Iowa, Iowa, United States of America
[c] Department of Pharmaceutical Services, Vanderbilt University Medical Center, Nashville, TN, United States of America
[d] Division of Infectious Diseases, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN, United States of America
[e] Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, United States of America

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ABSTRACT

Background: Therapeutic drug monitoring is used for aminoglycosides and vancomycin, and has been proposed for β-lactam antibiotics. Clinical blood samples in the ICU are often obtained via an existing vascular catheter rather than fresh needle phlebotomy. If antibiotics had previously been infused through a vascular catheter then used for blood sampling, carryover of antibiotic from the infusion to the sample might result in misleading assessments of target attainment. To address this concern we conducted a series of in vitro measurements of carryover for three commonly used antibiotics.

Methods: We infused piperacillin-tazobactam, meropenem, and cefepime at pharmacologic concentrations through commonly used vascular catheters at our hospital and flushed the catheters. We then aspirated warmed citrated bovine blood through each catheter and measured antibiotic concentrations in each aspirate.

Results: Carryover was below the limits of detection for piperacillin-tazobactam, meropenem, and vancomycin. Cefepime carryover, in contrast, was not negligible and needs to be investigated more fully.

Conclusion: Carryover from prior infusions does not appear to jeopardize measurements of piperacillin-tazobactam, meropenem, or vancomycin in commonly used vascular catheters at our institution. Caution in interpreting samples obtained for cefepime measurements appears advised until more data is available.

1. Introduction

Sepsis is common and deadly. Although there has been a movement to change the clinical definition recently, sepsis still describes a life-threatening systemic response to infection. Patients with sepsis complicated by organ dysfunction experience considerable morbidity and mortality. Sepsis affects more than a million patients in the United States annually, and rates are increasing. Cardiovascular dysfunction, or septic shock, affects > 500,000 patients annually in the United States, with mortality reportedly as high as 40% [1,2]. Treatment of sepsis consists of antibiotics, source control, and supportive care.

Early and appropriate antibiotics remain a mainstay of initial treatment of sepsis. The rationale for the appropriate criterion is obvious - the antibiotics should be effective against the presumed or confirmed organism. While some may define appropriate exclusively according to antimicrobial coverage, adequate concentration of antibiotics also fits within the appropriateness criterion. Since appropriate antibiotics remain one of the few mainstays of treatment, dosing of antibiotics remains vitally important. An antibiotic that treats an infection is only effective if the concentration is adequate. The Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016 state that best practice includes the use of dosing strategies for antibiotics based on pharmacokinetic/pharmacodynamic principles in patients with sepsis when such tests are available [3]. The focus of prior pharmacokinetic studies for these antibiotics has been in healthy populations and children rather than the critically ill population [4–6]. Antimicrobial pharmacokinetics in critical illness likely differ from those in patients without organ failure [7,8]. Dosing decisions based on the package insert alone may result in under- or over-dosing, motivating pharmacokinetic research into therapeutic drug monitoring of antibiotics besides vancomycin and aminoglycosides [8,9].

Phlebotomy in critically ill patients is often performed using existing vascular catheters that are also used for drug administration. Additional blood draws may be impossible to obtain. Sampling blood from an existing vascular catheter decreases patient discomfort and

* Corresponding author at: 1161 21st Avenue South MCN S3223, Nashville, TN 37232, United States of America.
E-mail address: william.fissell@vumc.org (W.H. Fissell).

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lowers barriers to enrollment in clinical studies. We sought to determine whether residual antibiotics retained in a vascular catheter affects measured antibiotic concentrations in samples drawn through the catheter, compared to the true value in blood.

Antibiotic solutions obtained from the hospital pharmacy (piperacillin-tazobactam, meropenem, cefepime and vancomycin) were infused in vitro through two central venous catheters and an arterial catheter commonly used in our hospital at the standard rates, concentrations, and volumes used in clinical practice. After infusions were complete, the catheters were flushed with 10 mL of 0.9% sodium chloride. Each catheter tip was then placed in warmed citrated bovine whole blood without any added antibiotic. 5 mL of blood was drawn and wasted, and then 10 mL blood samples were drawn through the catheter. Piperacillin, meropenem, cefepime and vancomycin concentrations in the bovine blood samples were measured by high-pressure liquid chromatography.

2. Materials and methods

2.1. Catheters

Three commonly used vascular catheters were tested. Triple-lumen central venous catheters are often the initial definitive access in sepsis and septic shock in the ICU. We tested our hospital's standard triple lumen catheter (Spectrum Central Venous Catheter, #G44128, Cook Medical, Bloomington, IN).

After initial stabilization it is common for the triple-lumen catheter to be withdrawn and a peripherally-inserted central catheter (PICC) is placed to facilitate infusions and phlebotomy. We tested two of the commonly used PICC access systems in our hospital. (Power PICC (dual-lumen, $n = 2$, #3295118 and single-lumen, $n = 1$, #3194118, Bard, Salt Lake City, UT). Dual- and single-lumen catheters were grouped together for statistical analysis.

Arterial catheters are occasionally used for hemodynamic monitoring and arterial blood gas sampling. While antibiotic infusion through an arterial catheter is very uncommon, it is possible that the catheter might be exposed to the antibiotic if it were used for sampling during an antibiotic infusion and then incompletely flushed. We tested the arterial catheter commonly used in our ICUs (Arrow Radial Arterial Catheterization Set with Integral Needle, RA-04020-SP, Arrow International, Reading, PA).

2.2. Antibiotic infusions

Concentrations, sources, and infusion rates of each antibiotic (Piperacillin-tazobactam, Meropenem, Vancomycin, and Cefepime) are tabulated in Table 1. For each experiment, a syringe pump (NE-1000, New Era Pump Systems, Farmingdale, NY) was programmed to infuse the antibiotic through the catheter at the prescribed rate and volume. Each catheter was connected to the infusion tubing and placed in a glass bowl in a water bath at 37 °C. After the infusion, the catheter was flushed with 10 mL 0.9% sodium chloride (BD 306547, Becton Dickinson, Franklin Lakes, NJ).

Table 1
Antibiotic Sources, Concentrations, and Infusion Rates. All antibiotics were diluted in 0.9% sodium chloride and drawn into a 60 mL syringe for infusion through the catheters using a syringe pump (see text). NDC, National Drug Codes.

Antibiotic	Source	Concentration	Infusion rate
Piperacillin-tazobactam	NDC 0206-8861-01, Pfizer, Philadelphia, PA	3.375 g/50 mL	12.50 mL/h
Meropenem	NDC 0264-3185-11, Braun Medical Inc., Bethlehem, PA	1 g/50 mL	16.67 mL/h
Vancomycin	NDC 0409-6535-01, Hospira Inc., Lake Forest, IL	1 g/250 mL	250 mL/1 h
Cefepime infusion	NDC 60505-6147-0, Apotex Corp., Weston, FL	2 g/50 mL	1.67 mL/min
Cefepime injection	NDC 60505-6147-0, Apotex Corp., Weston, FL	2 g/10 mL	2 mL/min

2.3. Blood sampling

For each replicate 5 mL of citrated bovine blood (7200806, Lampire Biological Products, Pipersville, PA) was drawn through each catheter into a sterile syringe and discarded. Using a new sterile 10 mL syringe (BD 309604, Becton Dickinson, Franklin lakes, NJ), another 10 mL of blood was drawn, placed in a 15 mL tube, and centrifuged at 3500*g* for 10 min. The catheter incubated for two minutes with blood in it, and then the saline flush was repeated. Another 5 mL of blood was drawn through the catheter and discarded. Using a new 10 mL syringe, another 10 mL of blood was aspirated and centrifuged at 3500*g* for 10 min. Plasma and ultrafiltrate (in Vivafree microcentrifuge filters with a 30 K MWCO) were prepared from the centrifuged samples for total and free antibiotic concentration measurement, respectively.

2.4. HPLC procedure used at Vanderbilt

The HPLC methods have been published previously for piperacillin-tazobactam, and the methods and approach for meropenem, cefepime, and vancomycin are exactly analogous (9). Certified reference antibiotic powders of tazobactam (PHR1686-1G, Sigma-Aldrich, St. Louis MO), piperacillin (PHR1805-1G, Sigma-Aldrich, St. Louis, MO), cefepime (USP Lot I0L200, Sigma-Aldrich, Rockville, MD), vancomycin (195,540 Lot Q4907, MP Biomedicals, Solon, OH) and meropenem (PHR1772-500MG, Sigma-Aldrich, St. Louis) were used as test analytes for calibrators and quality control (QC) materials. Penicillin G (MP Biomedicals 100543, Solon, OH) was used as an internal standard. Phosphate buffered saline (PBS) used in mobile phase and in calibrators was prepared from tablets (P4417-100 Tab, Sigma Aldrich St. Louis, MO). All water used for reagents was filtered using a Millipore Milli-Q system, however reagents that were not purchased pre-formulated or certified HPLC grade were filtered a second time using 0.22 μm filters (Corning/Millipore). Mobile phase A was prepared with above mentioned PBS tablets and Optima HPLC grade methanol (A454-4, Fisher Chemical Fairlawn, NJ). Mobile phase B of acetonitrile with 0.1%TFA was HPLC grade (Fisher). Acetonitrile for wash steps was also Optima HPLC grade (Fisher). Bovine plasma for QC levels was purchased as citrated whole bovine blood from (Lampire Biological Products, Pipersville, PA) and was prepared in Bio-one conical tubes (Greiner, Germany).

Calibrators were prepared by diluting stock solutions. These were made by accurately measuring powdered antibiotics. An equal volume of PBS was added to provide 1.0 mg/mL for piperacillin, cefepime, vancomycin and meropenem and 0.25 mg/mL for tazobactam. Stock solutions were maintained for 1 week at −80 °C. New calibrators were prepared every day using PBS to dilute to desired concentration. The ranges for standards start at the LLOQ of 0.5 mg/L for all antibiotics. Highest level standards vary based on clinical use of each drug: tazobactam 60 mg/L, cefepime 150 mg/L, vancomycin 80 mg/L, meropenem 100 mg/L and piperacillin 200 mg/L. Our ULOQ is 200 mg/L. Quality control materials were prepared by combining appropriate concentrations of antibiotic stock with citrated bovine plasma. Three levels were used, the lowest being 3.0 mg/L and the highest below ULOQ. 500 μL of QC material were added to VivaFree 30 K centrifuge filters (Sartorius Viva Products) and spun for 30 min at 2500*g* to remove large proteins and produce filtrate for analysis.

Chromatography was performed using an Agilent 1200 series HPLC system. Piperacillin, tazobactam and vancomycin concentrations were determined using a diode array detector (Agilent G1315C, Santa Clara, CA) with signals produced at 214 nm. Cefepime and meropenem were