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A novel way to investigate the effects of plasma exchange on antibiotic levels: use of microdialysis

Jason A. Roberts [a,b,*], Michael S. Roberts [c], Thomas A. Robertson [c], Sheree E. Cross [a,c], Jeffrey Lipman [a,b]

[a] *Burns, Trauma and Critical Care Research Centre, University of Queensland, Brisbane, Australia*
[b] *Intensive Care Unit, Royal Brisbane and Women's Hospital, Brisbane, Australia*
[c] *Therapeutics Research Unit, University of Queensland, Brisbane, Australia*

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Abstract

Plasma exchange (PE) is a treatment modality frequently used for many autoimmune diseases and may cause extracorporeal elimination of antibiotics. No data currently exist on antibiotic concentrations in extracellular fluid during PE. The aim of this study is to describe the effect of PE on the serum and subcutaneous tissue pharmacokinetics of piperacillin administered as a continuous infusion in a critically ill 17-year-old patient with Guillain–Barré syndrome and ventilator-associated pneumonia on Days 1 and 4 of antibiotic therapy. The effect of PE on piperacillin concentrations appears to be small. On Day 1, an estimated 7% of total piperacillin eliminated during PE was attributable to PE. On Day 4 this was estimated to be 11%. Using the in vivo sampling technique microdialysis, we have been able to show that a small redistribution of piperacillin from tissue to serum occurs in response to the reducing serum concentrations caused by PE. In critically ill patients, we believe that administration of a β-lactam antibiotic by continuous infusion should be considered to maintain serum and tissue concentrations of these time-dependent antibiotics.

Keywords: β-Lactam; Piperacillin; Continuous infusion; Plasma exchange; Microdialysis

1. Introduction

Plasma exchange (PE) is a treatment modality for many disease states, including metabolic, renal and autoimmune disorders such as Guillain–Barré syndrome (GBS) and myasthenia gravis [1,2]. It is a form of therapeutic apheresis used to remove plasma proteins, including immunoglobulins, from the body and to replace them with a fluid such as donor human albumin. PE is a procedure that may cause extracorporeal elimination of antibiotics and thus may affect antibacterial efficacy and therapeutic outcomes. The reporting of potential changes to antibiotic serum pharmacokinetics by PE is sparse at best. No known data have been published on changes to antibiotic levels in extracellular fluid (ECF) of tissues during PE. The consensus of the published literature, which consists of case reports and small clinical studies, is that drugs with a volume of distribution (V_d) consistent with total body water (0.3 L/kg) and high protein binding are most likely to require dosing adjustments as a result of PE [3,4].

Developing an understanding of the impact of treatment modalities such as PE on antibiotic pharmacokinetics can enable the procurement of dosing regimens that optimise antibiotic therapy. For time-dependent antibiotics like the β-lactams, administration by continuous infusion may mitigate any extracorporeal clearance by PE [5]. Optimised dosing is particularly important in critically ill patients where the effect of early and appropriate antibiotic therapy for reducing infection-related morbidity and mortality is well characterised [6–11]. Furthermore, during critical illness, β-lactams may have impaired tissue penetration [12], which

* Corresponding author. Present address: Burns Trauma and Critical Care Research Centre, Level 3 Ned Hanlon Building, Royal Brisbane and Women's Hospital, Butterfield Street, Brisbane, Queensland 4029, Australia. Tel.: +61 7 3636 4108; fax: +61 7 3636 3542.
E-mail address: j.roberts2@uq.edu.au (J.A. Roberts).

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may be a significant issue as the focus of most infections is probably ECF [13]. Concentration changes of an antibiotic in tissue, or the 'active site', can be measured using an in vivo sampling technique called microdialysis. Microdialysis catheters can be inserted subcutaneously and allow diffusion of small molecules such as antibiotics across a semipermeable membrane for collection and subsequent quantification. Knowledge of changes to tissue concentrations is essential for predicting the clinical implications of PE on antibiotic therapy.

We report the first case of concurrent serum and tissue antibiotic concentration changes during treatment with PE.

2. Materials and methods

2.1. Patient characteristics

A 17-year-old male (height 176 cm; weight 80 kg; body surface area 1.98 m^2) was diagnosed with GBS and admitted to a tertiary Intensive Care Unit (ICU) for intubation for declining respiratory muscle function. The patient was receiving intermittent PE as a treatment for GBS. On Day 3 of ICU admission the patient developed aspiration pneumonia. An endotracheal tube aspirate was sampled and sent to the local Microbiology Department. Upon diagnosis of aspiration pneumonia, the patient displayed signs consistent with sepsis [14] (white cell count 13.8×10^9/L; heart rate 127 beats per min; temperature 38.5 °C; partial pressure of oxygen in arterial blood/fractional concentration of inspired oxygen (PaO_2/FiO_2) 136) for which treatment with piperacillin/tazobactam was empirically commenced. As part of a randomised controlled microdialysis study investigating tissue penetration of piperacillin administered by continuous or bolus administration, permission to take blood and microdialysis samples was obtained from the patient's legally authorised representative.

After 48 h of incubation, the microbiologist reported growth of scant Gram-positive cocci and scant Gram-negative bacilli. No susceptibilities to piperacillin or tazobactam were reported. The patient completed a 5-day course of piperacillin/tazobactam, with complete clinical resolution of pneumonia. After 2 weeks, the patient's respiratory function improved and he was discharged from the ICU to a medical ward for ongoing care of GBS, which improved over the ensuing weeks.

2.2. Antibiotic dose and administration

Continuous infusion dosing for piperacillin/tazobactam was as follows: Day 1, 4 g/0.5 g piperacillin/tazobactam bolus infusion (over 20 min) followed immediately by a continuous 24-h infusion of 8 g piperacillin/1 g tazobactam (piperacillin 333 mg/h); and Day 2 onward, 12 g/1.5 g piperacillin/tazobactam administered by 24-h infusion (piperacillin 500 mg/h).

2.3. Plasma exchange

PE was performed with a COBE Spectra Blood Cell Separator (COBE BCT, Lakewood, CO) on Days 1 and 4 of piperacillin/tazobactam treatment. PE continued for 97 min on Day 1 with 80 mL of plasma exchanged per min. In total, 2903 mL of plasma was exchanged and replaced with donor serum albumin. On Day 4 of piperacillin/tazobactam treatment, PE continued for 96 min. However, because the vascular access occluded after 66 min, no more exchange occurred. In total 2054 mL of plasma and donor serum albumin were exchanged on Day 4. Multiple serum samples were taken on Days 1 and 4 to measure the serum concentration of piperacillin.

2.4. Microdialysis

The principles and details of microdialysis have been described previously [15]. Briefly, microdialysis is based on sampling of analytes from the extracellular space by diffusion across a semipermeable membrane. In vivo, this process is accomplished by constantly perfusing the microdialysis probe with a physiological solution at a low flow rate. Once the probe is implanted in tissue, analytes diffuse across the membrane from the ECF into the perfusate and may be sampled and analysed. In this patient, a microdialysis probe (CMA 60; Microdialysis AB, Stockholm, Sweden) with a molecular weight cut-off of 20 kDa, an outer diameter of 0.6 mm and a membrane length of 30 mm was aseptically placed in the subcutaneous tissue of the upper right arm. The probe was perfused with benzyl penicillin 2 μg/mL (internal standard) in 0.9% sodium chloride at a flow rate of 1.6 μL/min [16]. After commencement of the piperacillin/tazobactam infusion, microdialysis samples were collected at ca. 20-min intervals on Days 1 and 4 of antibiotic treatment.

2.5. Drug assay

Serum piperacillin concentrations were measured using high-performance liquid chromatography (HPLC) with ultraviolet detection (Waters HPLC (Milford, MA) with C18 column (Phenomenex, NSW, Australia) with 510 pump, 717 autosampler and 486 Tunable Absorbance Detector set at 218 nm λ) using an acetonitrile phosphate buffer gradient. Microdialysate concentrations of piperacillin were analysed with a HPLC system with Electrospray Mass Spectrometer detector (Applied Biosystems API3000 Tandem MS System (Foster City, CA); Shimadzu HPLC (Rydalmere, NSW, Australia) with Phenomenex Gemini C18 column). Results were interpreted using Analyst™ software.

2.6. Pharmacokinetic calculations

The following pharmacokinetic parameters during PE were determined using the following equations.