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Short communication

Pharmacokinetics of meropenem and piperacillin in critically ill patients with indwelling surgical drains

Syamhanin Adnan[a,b,*], Janice Xuanhui Li[c], Steven C. Wallis[a], Michael Rudd[a,d], Paul Jarrett[a], David L. Paterson[b,e], Jeffrey Lipman[a,f], Andrew A. Udy[a,f], Jason A. Roberts[a,f,g]

[a] Burns, Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Australia
[b] University of Queensland Centre for Clinical Research, The University of Queensland, Brisbane, Australia
[c] School of Pharmacy, The University of Queensland, Brisbane, Australia
[d] Department of Surgery, Royal Brisbane and Women's Hospital, Brisbane, Australia
[e] Department of Infectious Diseases, Royal Brisbane and Women's Hospital, Brisbane, Australia
[f] Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, Australia
[g] Pharmacy Department, Royal Brisbane and Women's Hospital, Brisbane, Australia

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ABSTRACT

Meropenem and piperacillin are two commonly prescribed antibiotics in critically ill surgical patients. To date, the pharmacokinetics of these antibiotics in the presence of indwelling abdominal surgical drains is poorly defined. This was a prospective pharmacokinetic study of meropenem and piperacillin. Serial plasma, urine and surgical drain fluid samples were collected over one dosing interval of antibiotic treatment in ten patients (meropenem, $n = 5$; piperacillin $n = 5$). Drug concentrations were measured using a validated high-performance liquid chromatography assay. Median (interquartile range) pharmacokinetic parameter estimates for meropenem were as follows: area under concentration–time curve (AUC), 128.7 mg h/L (95.3–176.7 mg h/L); clearance (CL), 5.7 L/h (5.1–10.5 L/h); volume of distribution (V_d), 0.41 L/kg (0.35–0.56 L/kg); AUC ratio (drain:plasma), 0.2 (0.1–0.2); and calculated antibiotic clearance via surgical drain, 3.8% (2.8–5.4%). For piperacillin, unbound pharmacokinetic results were as follows; AUC, 344.3 mg h/L (341.1–348.4 mg h/L); CL, 13.1 L/h (12.9–13.2 L/h); V_d, 0.63 L/kg (0.38–1.28 L/kg); AUC ratio (drain:plasma), 0.2 (0.2–0.3); and calculated antibiotic clearance via surgical drain 8.2% (3.3–14.0%). A linear correlation was present between the percentage of antibiotic cleared through the drain and the volume of surgical drain fluid output for meropenem ($r^2 = 0.89$; $P = 0.05$) and piperacillin ($r^2 = 0.63$; $P = 0.20$). Meropenem and piperacillin have altered pharmacokinetics in critically ill patients with indwelling surgical drains. We propose that only when very high drain fluid output is present (>1000 mL/day) would an additional dose of antibiotic be necessary.

1. Introduction

Meropenem and piperacillin/tazobactam (TZP) are commonly prescribed for post-operative infections in critically ill patients. Surgical drains may be inserted for either therapeutic, prophylactic or decompressive drainage of excess air or fluid or to monitor production of wound exudate post surgery [1].

During clinical practice at our tertiary referral intensive care unit (ICU), we have observed that critically ill patients with indwelling surgical drains have lower plasma concentrations of antibiotics than other comparable patients [2]. There are few data available to suggest whether these surgical drains are associated with subtherapeutic concentrations, which may lead to impaired antibiotic efficacy. Most of the studies documenting the concentrations of antibiotics in intra-abdominal and pleural fluid primarily describe antibiotic penetration and do not examine whether these surgical drains are a mechanism for increased drug clearance. There are also limited data on the time course profile of both meropenem and piperacillin in patients with surgical drains. This lack of data limits the ability to predict dosing requirements for such patients [3–5].

The importance of achieving adequate antibiotic concentrations at the site of infection is well recognised, with subtherapeutic concentrations hypothesised to be associated with therapeutic failure [6]. However, measurement of drug concentrations at the site of infection is often not feasible, and plasma drug concentrations remain an important surrogate.

The target exposure for antibiotics is guided by the minimum inhibitory concentration (MIC) of the target bacterial pathogen.

* Corresponding author. Present address: Burns, Trauma and Critical Care Research Centre, Level 7, Block 6, Royal Brisbane and Women's Hospital, Brisbane, QLD 4029, Australia. Tel.: +61 7 3346 4932; fax: +61 7 3365 5192.
E-mail address: s.adnan@uq.edu.au (S. Adnan).

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For β-lactam antibiotics, bacterial killing depends largely on the time the free (or unbound) antibiotic concentration remains above the MIC, i.e. $fT_{>MIC}$. The specific percentage of the dosing interval differs between β-lactam classes, i.e. 40% for carbapenems, 50% for cephalosporins and 60–70% for penicillins [7]. The primary aim of this project was to describe the pharmacokinetics of both meropenem and piperacillin in critically ill patients with indwelling surgical drains with a focus on describing drug clearance through the drains.

2. Materials and methods

This was a prospective, open-labelled, pharmacokinetic study conducted at the ICU of Royal Brisbane and Women's Hospital (Brisbane, Australia). Critically ill patients who met the following criteria were eligible for inclusion: (a) written informed consent had been obtained from the patient or his/her substitute decision-maker; (b) presence of at least one indwelling surgical drain actively producing fluid (defined as > 10 mL in the preceding 6 h); (c) clinical indication for meropenem or TZP therapy; and (d) an intra-arterial catheter in situ (for the purposes of blood sampling). Patients were excluded from the study if one or more of the following criteria were met: (a) renal impairment, defined as plasma creatinine concentration > 170 μmol/L; (b) pregnancy; or (c) admission following burns injury.

2.1. Antibiotic administration and sample collection

All samples were collected over a single dosing interval. Standard doses were administered [1 g intravenous (i.v.) every 8 h for meropenem and 4.5 g i.v. every 6 h for TZP]. Blood samples were drawn at seven time points. For meropenem, this was at 0 (pre dose), 0.5 h (end of infusion), 1, 1.5, 2, 4 and 8 h post dose. For TZP, this was at 0 (pre dose), 0.5 h (end of infusion), 1, 1.5, 2, 4 and 6 h post dose. Surgical drain fluid was collected from the indwelling surgical drain every hour during the dosing interval. Urine samples were collected from indwelling urinary catheters every hour during the dosing interval.

All samples were immediately placed in polypropylene tubes on ice and were centrifuged at 3000 rpm for 10 min within 4 h of collection. The plasma and supernatant were removed and aliquots of the plasma were placed into labelled polypropylene screw-cap cryovials and stored at −80 °C until assay.

2.2. Assay

Meropenem and piperacillin in plasma, surgical drain fluid and urine were measured by high-performance liquid chromatography with ultraviolet detection (HPLC-UV) on a Shimadzu Prominence instrument (Shimadzu Corp., Kyoto, Japan). All samples were assayed alongside calibration standards and quality controls prepared by spiking drug into matching drug-free biological matrix (surgical drain fluid samples were treated as plasma samples as they are both proteinaceous matrices and no drug-free drain fluid was available). Assays were validated and conducted using criteria from the US Food and Drug Administration (FDA) guidance on bioanalysis [8].

To measure unbound piperacillin concentrations, the unbound fraction was obtained by ultrafiltration of plasma at 37 °C using Millipore Centrifree® 30 kDa molecular weight cut-off centrifugal filter units (Merck, Tullagreen, Ireland) for 5 min at 1410 × *g* so that only 15–40% of the plasma volume was filtered to prevent perturbation of the binding equilibrium. Unbound concentrations were not measured for meropenem as plasma protein binding is only 2%, which was considered not significant.

The precision and accuracy of the methods were validated to be within 6% (total meropenem in plasma/surgical drain fluid from 0.2 to 50 mg/L), 3% (meropenem in urine from 10 to 2000 mg/L), 10% (total piperacillin in plasma/surgical drain fluid from 0.5 to 500 μg/mL), 6% (unbound piperacillin in plasma from 1 to 500 mg/L) and 6% (piperacillin in urine from 100 to 40 000 mg/L) at low, medium and high concentrations of the calibration range.

2.3. Pharmacokinetic analysis

A non-compartmental pharmacokinetic analysis was performed to describe the disposition of meropenem and piperacillin in critically ill patients with indwelling surgical drains. The C_{max} was the observed maximum concentration at the end of infusion, and the trough concentration (C_{min}) was the observed minimum concentration prior to drug administration. The area under the concentration–time curve (AUC) from 0 to 8 h for meropenem and from 0 to 6 h for piperacillin was calculated using the trapezoidal rule. The AUC extrapolated to infinity ($AUC_{0-\infty}$) was calculated using AUC and the elimination rate constant (k_{el}). The k_{el} was calculated as the negative slope of the non-weighted squares curve fit of the final three sampling points during the elimination phase. The percentage of antibiotic cleared through the surgical drain was calculated with the following equation: $(C_{drain\ (total)}/volume_{drain\ (total)})$/dose, where C_{drain} is the concentration in the drain. Clearance (CL) was calculated as dose/$AUC_{0-\infty}$. The volume of distribution (V_d) was calculated as CL/k_{el}. The half-life was calculated at 0.693/k_{el}.

2.4. Statistical analysis

Statistical analysis was performed using GraphPad Prism v.5.0 (GraphPad Software Inc., La Jolla, CA). Linear regression on the percentage of antibiotic clearance through the surgical drain and the volume of surgical drain fluid output was performed. *P*-values of < 0.05 were considered significant.

3. Results

Ten patients were included in this study (meropenem, $n = 5$; TZP, $n = 5$). The mean ± standard deviation patient age was 69 ± 15 years, weight 75 ± 23 kg, Acute Physiology and Chronic Health Evaluation (APACHE) II score 11 ± 2 and Sequential Organ Failure Assessment (SOFA) score 3 ± 2. Five (50%) of the patients were male; nine patients had intra-abdominal drains, whilst the other patient had a left leg drain because of severe lower limb trauma.

Fig. 1 displays the concentration–time profiles for meropenem and piperacillin both in plasma and drain fluid. Both plasma and drain concentrations of meropenem were above the European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC breakpoint of *Pseudomonas aeruginosa* (2 mg/L), but this was not achieved for the piperacillin breakpoint (16 mg/L) [9]. However, the observed concentrations were above the EUCAST MIC breakpoint for Enterobacteriaceae for both drugs (2 mg/L for meropenem and 8 mg/L for piperacillin) [9].

Table 1 gives the pharmacokinetic parameters for meropenem and piperacillin. These data are contrasted against published data from healthy volunteers [10,11]. Both drugs show a larger V_d in the studied patients compared with healthy volunteers. CL of meropenem is 50% lower than in healthy volunteers, but CL is only slightly lower for piperacillin. The estimated percentage of antibiotic cleared through the surgical drains, whilst not clinically significant, was still notable (3.8% and 8.2% for meropenem and piperacillin, respectively).

Linear regression analyses of the percentage of antibiotic cleared through the surgical drain and the volume of surgical drain fluid are shown in Fig. 2. Correlations were observed for meropenem