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Pharmacodynamic profiling of intravenous antibiotics against prevalent Gram-negative organisms across the globe: the PASSPORT Program—Asia-Pacific Region

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ABSTRACT

Due to escalating antimicrobial resistance amongst Gram-negative organisms, the choice of effective empirical antimicrobial regimens has become challenging. Monte Carlo simulations were conducted for conventional and prolonged infusion regimens of doripenem, imipenem and meropenem using pharmacokinetic data from adult patients with conserved renal function. Minimum inhibitory concentration data against *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* were incorporated from the COMPACT surveillance programme in the Asia-Pacific region of the world. The cumulative fraction of response (CFR) was determined for each regimen against each bacterial population. All simulated carbapenem regimens achieved an optimal CFR against *E. coli* and *K. pneumoniae* (94.5–100% CFR). Against *P. aeruginosa*, doripenem achieved 78.7–92.6% CFR, imipenem achieved 60.4–79.0% CFR and meropenem achieved 73.0–85.1% CFR. The only dosing regimen to achieve ≥90% CFR against *P. aeruginosa* was doripenem 1000 mg and 2000 mg every 8 h (4-h infusion). Carbapenem CFRs against *A. baumannii* were much lower (29.2–54.4% CFR). CFRs for non-fermenting isolates were ca. 10% lower for isolates collected in the Intensive Care Unit. Carbapenem resistance amongst Enterobacteriaceae remains low in the Asia-Pacific region and thus standard carbapenem dosing regimens had a high likelihood of achieving pharmacodynamic exposures. However, larger doses combined with prolonged infusion will be required to increase the CFR for these carbapenems against resistant non-fermenting Gram-negatives that are common in these countries. The safety and efficacy of these high dosing regimens will need to be confirmed in the clinical setting.

1. Introduction

In the nosocomial setting, resistance amongst Gram-negative bacteria continues to be a challenge facing clinicians [1]. As an illustration of these difficulties, the Infectious Diseases Society of America (IDSA) has outlined the problem organisms in today's medical centres by the acronym ESKAPE, which encompasses extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli*, meticillin-resistant *Staphylococcus aureus* (MRSA), ESBL- and/or carbapenemase-producing *Klebsiella* spp., *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and enterococci or ESBL-producing *Enterobacter* spp. [2]. Five of these seven highlighted organisms are Gram-negatives; moreover, the prevalence of Gram-negative infections is once again rising. In an international study of 13 796 patients, 62% of positive cultures were Gram-negatives, with *P. aeruginosa* isolated in 19.9% of all infections [3]. Resistance amongst these organisms is increasing, with the proportion of carbapenem- and fluoroquinolone-resistant *P. aeruginosa* isolates rising to ca. 15–25% in the USA [4–6]. *Acinetobacter* spp. are frequently multidrug-resistant, with only the carbapenems, aminoglycosides and polymyxins commonly retaining activity against this pathogen [4,7]. Notably, resistance outside the USA, particularly in the Asia-Pacific region, is often much greater. Surveillance data from the Asia-Pacific rim have demonstrated carbapenem resistance of well over 20% for the non-fermenting Gram-negatives as well as a high prevalence of ESBL-producing *E. coli* and *Klebsiella*

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spp. amongst the Enterobacteriaceae [8,9]. Owing to large variations in resistance, knowledge of regional rates is paramount when selecting empirical antibiotic therapy.

In addition to selecting the proper antibiotic based on local resistance trends, using the correct dosage is important for achieving optimal pharmacodynamic exposures. Pharmacodynamic studies have demonstrated that β-lactams require free drug concentrations to exceed the minimum inhibitory concentration (MIC) of the organism for ≥40% of the dosing interval in order to achieve bactericidal effects [10]. Previous pharmacodynamic studies have determined the likelihood of specific carbapenem regimens achieving the requisite pharmacodynamic exposure using Gram-negative isolates from North America, South America and Europe [11–16]. These studies have consistently observed that the carbapenems retain a high likelihood of achieving bactericidal exposure against these bacteria. Unfortunately, past studies have not included doripenem, the most recent addition to the Gram-negative armamentarium. Therefore, the PASSPORT (Probability of target attainment of Antibacterial agent Studied for Susceptibility and Pharmacodynamic Optimization in Regional Trials) Program was designed to compare doripenem with other carbapenems in order to determine the best strategy for achieving maximal pharmacodynamic activity against contemporary Gram-negative organisms regionally [17]. The PASSPORT data from the Asia-Pacific region are presented here.

2. Materials and methods

2.1. Antimicrobials and pharmacokinetic models

The following intravenous carbapenem regimens were simulated as 30-min infusions: imipenem/cilastatin 0.5 g every 6 h (q6h) and every 8 h (q8h) and 1 g q8h; and meropenem 0.5 g q6h and 0.5, 1 and 2 g q8h. The following regimens were simulated as 1-h infusions: doripenem 0.5, 1 and 2 g q8h. In addition, prolonged infusion (PI) regimens were also included: doripenem 0.5, 1 and 2 g q8h as a 4-h PI; imipenem/cilastatin 0.5 g q6 h and q8h (3-h PI) and 1 g q8h (3-h PI); and meropenem 0.5, 1 and 2 g q8h (3-h PI).

Data from population pharmacokinetic studies in infected and/or critically ill patients [18–20] were used, as has previously been described in PASSPORT publications [17]. The methodology used to simulate steady-state antibacterial exposures in adult patients with conserved renal function (i.e. ≥50 mL/min) can also be found elsewhere [14].

2.2. Microbiology

Microbiological data were obtained from the COMPACT (Comparative Activity of Carbapenem Testing Study) Asia-Pacific surveillance programme for 253 *E. coli*, 232 *Klebsiella pneumoniae*, 780 *P. aeruginosa* and 128 *A. baumannii* for 2009. Available data from 27 centres in eight Asia-Pacific countries (Australia, Hong Kong, India, Indonesia, Malaysia, Philippines, Singapore and Thailand) were included. Isolates were collected from patient specimens and were submitted to a reference laboratory for species confirmation. Antimicrobial susceptibility testing was conducted at the collecting centres by Etest according to the manufacturer's instructions (AB bioMérieux, Solna, Sweden). Susceptibility of Enterobacteriaceae to doripenem, imipenem and meropenem was classified according to the most up-to-date Clinical and Laboratory Standards Institute (CLSI) published interpretive criteria (MIC ≤1 μg/mL) [21]. For *P. aeruginosa* and *A. baumannii*, imipenem and meropenem susceptibility were classified according to CLSI published interpretive criteria (MIC ≤ 4 μg/mL) [21], whereas US Food and Drug Administration (FDA) susceptibility breakpoints were applied for doripenem (*P. aeruginosa*, MIC ≤ 2 μg/mL; *A. baumannii*, MIC ≤ 1 μg/mL) as no CLSI criteria are available for this compound [22].

2.3. Monte Carlo simulation

A 5000-patient Monte Carlo simulation (Crystal Ball 2000; Decisioneering Inc., Denver, CO) was conducted to estimate the steady-state concentration–time profile of each regimen. During simulations, pharmacokinetic parameters and dispersion were assumed to follow log-Gaussian distributions. Covariance amongst pharmacokinetic parameters was also applied during simulations. The unbound fraction of the drug concentration was simulated as a uniform distribution whereby any value in the simulated range had an equal probability of occurring based on a range of values found in the literature or package insert.

Pharmacodynamic exposures for the simulated carbapenem regimens were assessed as 40% free time above the MIC ($fT > MIC$) [10]. The probability of target attainment (PTA) was calculated for each dosage regimen over a range of doubling MICs between 0.008 μg/mL and 256 μg/mL. The PTA is the likelihood that the antimicrobial regimen will meet or exceed the pre-defined pharmacodynamic target at a specific MIC.

PTAs for each regimen were used to calculate the cumulative fraction of response (CFR) for each antibiotic regimen against the bacterial population. The CFR is the probability that the regimen will attain its pharmacodynamic index against the entire population of organisms. The CFR was calculated as the summation of $PTA_i \times F_i$, with the subscript i indicating the MIC category ranked from lowest to highest MIC value of a population of microorganisms, PTA_i being the PTA of each MIC category for that drug regimen, and F being the fraction of the population of microorganisms at each MIC category. A CFR of ≥90% was applied for defining a regimen as optimal against a bacterial population. The CFR was calculated for each antibiotic regimen/bacterial population as well as for isolates collected inside versus outside of the Intensive Care Unit (ICU). Finally, for *P. aeruginosa*, data were split by source of infection for comparison (bloodstream versus respiratory versus intra-abdominal).

3. Results

The MICs for 50% and 90% of the organisms (MIC_{50} and MIC_{90} values, respectively) and the percent susceptibility to the three carbapenems and the collection sources for the isolates are presented in Tables 1 and 2, respectively. Susceptibility rates for *E. coli* and *K. pneumoniae*, regardless of ICU versus non-ICU source, were >98% for all carbapenems tested. For *P. aeruginosa*, carbapenem susceptibilities declined by ca. 8–10% when comparing ICU isolates with the cumulative MICs. Similarly, carbapenem susceptibilities also declined for *A. baumannii* from ca. 30–33% to ca. 19–22% in the ICU.

A summary of CFR for the carbapenem regimens against the total isolate populations is presented in Table 3. All simulated carbapenem regimens obtained optimal exposures against *E. coli* and *K. pneumoniae* populations. Against *P. aeruginosa*, only PI of doripenem 1 g and 2 g q8h obtained a CFR ≥ 90%. Owing to very high MICs, no regimens obtained optimal CFR against *A. baumannii*.

CFR results for ICU versus non-ICU isolates are presented in Table 4 for *P. aeruginosa* and *A. baumannii*. There were no differences in CFR between ICU and non-ICU isolates for any regimens against *E. coli* and *K. pneumoniae* (data not shown). Amongst *P. aeruginosa* and *A. baumannii* isolates collected in the ICU compared with outside the ICU, there were clear differences (ca. 10–20%) in CFR amongst regimens in favour of non-ICU isolates. The majority of carbapenem regimens, with the exception of low doses of