Assessing the pharmacodynamic profile of intravenous antibiotics against prevalent Gram-negative organisms collected in Colombia

ABSTRACT

Objectives: This study was designed to simulate standard and optimized dosing regimens for intravenous antibiotics against contemporary populations of *Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii,* and *Pseudomonas aeruginosa* using MIC distribution data to determine which of the tested carbapenem regimens provided the greatest opportunity for obtaining maximal pharmacodynamic (PD) activity. **Methods:** The isolates studied were obtained from the COMPACT-COLOMBIA surveillance program conducted between February and November 2009. Antimicrobial susceptibility testing was conducted by broth microdilution method according to the CLSI guidelines. Doripenem, imipenem-cilastatin, and meropenem, were the modeled antibiotics. A 5,000 patient Monte Carlo simulation was performed for each regimen and PD targets were defined as free drug concentrations above the MIC for at least 40% of the dosing interval. **Results:** All carbapenem regimens obtained optimal exposures against *E. coli*, unlike the other Enterobacteriaceae tested. Against *P. aeruginosa*, only a prolonged infusion of doripenem exceeded the 90% cumulative fraction of response (CFR) threshold. Worrisomely, no regimens for any of the drugs tested obtained optimal CFR against *A. baumannii*. For *P. aeruginosa* intensive care unit (ICU) isolates, CFR was approximately 20% lower for isolates collected in the respiratory tract compared with bloodstream or intra-abdominal for imipenem and meropenem. Noteworthy, all doripenem and meropenem regimens achieved greater than 90% CFR against bloodstream and respiratory isolates of *K. pneumoniae*. **Conclusions:** Our data suggests that higher dosing and prolonged infusion of doripenem or meropenem may be suitable for empirically treating ICU *P. aeruginosa*, while none of the carbapenems achieved optimal cumulative fraction of response against *A. baumannii*. Standard dosing regimens of all the carbapenems tested achieved optimal CFR against *E. coli* isolates, but higher carbapenem dosages might be required for empiric treatment of *K. pneumoniae*, particularly from an intra-abdominal source. Non-standard dosage regimens studied in this modeling should be proven effective in prospective clinical trials.

Keywords: drug resistance, bacterial; Gram-negative bacteria; Monte Carlo Method; Colombia; pharmacology.

INTRODUCTION

There is tremendous variability in antimicrobial resistance not only amongst pathogens causing various clinical infections in different geographic regions. Therefore, continuous surveillance of the extent and trends of antimicrobial resistance is necessary. Infections produced by Gram-negative bacilli (i.e. *Escherichia coli* and *Klebsiella pneumoniae*) and non-fermenters (i.e. *Acinetobacter baumannii* and *Pseudomonas aeruginosa*) continue to be of key importance in the Intensive Care Unit (ICU), as they have been considered important determinants of hospital mortality, prolonged hospitalization and increased health-care costs as compared to infections caused by non-resistant bacteria.

Alarmingly, a limited number of antimicrobials retain some potency against these increasing resistant pathogens and novel therapies currently in the developmental pipeline appears to be years away from the wide scale clinical use. Hence, it is crucial to employ these currently available agents responsibly and effectively to extend their usefulness for the coming years.

The potency/effectiveness of antimicrobial therapy may be considered in terms of their *in vitro* and *in vivo* activity against the microorganism of interest. To maximize the probability

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of successful outcomes against theses difficult pathogens, several strategies have been utilized including combination therapy and/or pharmacodynamic (PD) optimization. The latter approach has become increasingly utilized in the clinical setting as a means of achieving maximal bacteria kill and reducing the risk of the emergence of resistant bacteria. Therefore, once the decision regarding the choice of antimicrobial has been made, it is necessary to ensure that the dose, frequency of administration, and duration over which the agent is infused are optimized.

The aim of the PASSPORT (**P**robability of target attainment of **A**ntibacterial agents **S**tudied for **S**usceptibility and **P**harmacodynamic **O**ptimization in **R**egional **T**rials) program is designed to simulate standard and optimized dosing regimens for common intravenous antibiotics against contemporary populations of *E. coli*, *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa* using MIC distribution data from isolates collected across the globe. In this report, isolates collected during the COMPACT (Comparative Activity of Carbape em Testing E-test studying)-COLOMBIAN surveillance study were analyzed to determine which of the tested carbapenem regimens provided the greatest opportunity for pharmacodynamic optimization. The COMPACT-COLOMBIAN surveillance study was carried out by The International Center for Medical Research and Training (CIDEIM) with the objective of increasing the knowledge on the susceptibility to antibiotics of Gram-negative bacteria causing serious infections in hospitalized patients.

MATERIALS AND METHODS

Antimicrobials

Antimicrobials were included in the pharmacodynamic model if they had comparative minimum inhibitory concentration (MIC) data available from the COMPACT-COLOMBIAN study. The following intravenous carbapenem regimens were modeled:

- doripenem 500 mg, 1,000 mg, and 2,000 mg every 8 hours (1-hour and 4-hour infusions)
- imipenem-cilastatin 500 mg every 6 and 8 hours (0.5-hour and 3-hour infusions); 1,000 mg every 8 hours (0.5 hour and 3 hour infusions)
- meropenem 500 mg every 6 hours (0.5-hour infusions); 500 mg, 1,000 mg, and 2,000 mg every 8 hours (0.5-hour and 3-hour infusions)

Pharmacokinetic models

Steady-state exposures for each carbapenem were determined using pharmacokinetic parameter estimates obtained from published population pharmacokinetic studies undertaken in infected and/or critically ill adult patients.[1,2] The methods used to simulate these antibiotic exposures in adult patients with conserved renal function (i.e. creatinine clearance ≥ 50 mL/min) have been previously described.[3]

Monte Carlo simulation

A 5,000 patient Monte Carlo simulation (Crystal Ball 2000; Decisioneering Inc., Denver, CO) was performed for each regimen, and the probability of a simulated patient achieving the pharmacodynamic target, referred to as probability of target attainment (PTA), was calculated over a range of doubling MICs between 0.06 and 64 μg/mL. Pharmacodynamic targets were defined as free drug concentrations above the MIC ($fT > MIC$) for at least 40% of the dosing interval.[4]

PTAs for each regimen were used to calculate the cumulative fraction of response (CFR) for each antibiotic regimen against the bacteria population. The CFR was calculated as the summation of $PTA_i{*}F_i$, 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, the fraction of the population of microorganisms at each MIC category. A CFR of at least 90% was applied for defining a regimen as optimal against a bacterial population.

Microbiology

In the present study, the 81 *E. coli*, 163 *K. pneumoniae*, 124 *P. aeruginosa*, and 34 *A. baumannii* isolates were obtained from the COMPACT-COLOMBIA surveillance program coordinated in Cali, Colombia by CIDEIM. These isolates were collected at CIDEIM between February and November 2009 from 12 hospitals in Colombia. Characteristics and counts of these isolates are provided in Table 1. Antimicrobial susceptibility testing was conducted by broth microdilution method according to the CLSI guidelines using Sensititre plates produced by TREK Diagnostic Systems, Inc. (Westlake, OH, USA). The susceptibility of doripenem, imipenem, and meropenem against Enterobacteriaceae was classified according to the most up-to-date Clinical Laboratory Standards Institute (CLSI) published interpretive criteria (MIC ≤ 1 μg/mL).[5] For *P. aeruginosa* and

Table 1. Numbers of isolates collected during COMPACT-COLOMBIA

Isolate	*E. coli*	KPN	PSA	AB
Total No.	81	163	124	34
ICU isolate No.	28	86	81	26
No. by source:				
Bloodstream	33	92	54	18
cIAI	43	29	27	5
NP	4	42	43	11

KPN, *K. pneumoniae;* PSA, *P. aeruginosa*; AB, *A. baumannii*; No., number; ICU, intensive care unit; cIAI, complicated intra-abdominal infection; NP, nosocomial pneumonia isolate.

A. baumannii, the susceptibility of imipenem and meropenem was classified according to CLSI published interpretive criteria (MIC ≤ 4 μg/mL), whereas U.S. 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 currently available for this compound.[5,6] The MIC_{50}, MIC_{90} and percent susceptibility for the three carbapenems are presented in Table 2.

Table 2. MIC_{50}, MIC_{90}, and antimicrobial susceptibility for doripenem, imipenem, and meropenem against* E. coli, K. pneumoniae, P. aeruginosa, *and* A. baumannii *collected from COMPACT-COLOMBIA

Organism (No.) Antibiotic	MIC_{50}	MIC_{90}	Susceptibility (%)
Total isolates			
E. coli (81)			
Doripenem	≤ 0.125	0.25	97.5
Imipenem	0.25	1	90.1
Meropenem	≤ 0.06	0.25	96.3
K. pneumoniae (163)			
Doripenem	≤ 0.125	2	87.1
Imipenem	0.5	8	81.0
Meropenem	≤ 0.06	4	86.5
P. aeruginosa (124)			
Doripenem	0.5	16	71.0
Imipenem	2	64	68.6
Meropenem	1	32	72.6
A. baumannii (34)			
Doripenem	> 16	> 16	44.1
Imipenem	> 8	> 8	44.1
Meropenem	> 8	> 8	44.1
ICU isolates			
E. coli (28)			
Doripenem	≤ 0.125	0.5	96.4
Imipenem	0.25	2	89.3
Meropenem	≤ 0.06	1	92.9
K. pneumoniae (86)			
Doripenem	≤ 0.125	0.5	94.2
Imipenem	0.5	2	86.1
Meropenem	≤ 0.06	0.5	93.0
P. aeruginosa (81)			
Doripenem	0.5	16	67.9
Imipenem	4	64	66.7
Meropenem	1	32	70.4
A. baumannii (26)			
Doripenem	> 16	> 16	30.7
Imipenem	> 8	> 8	30.7
Meropenem	> 8	> 8	30.7

No., number; ICU, intensive care unit.

Detailed MIC distributions for each carbapenem against *P. aeruginosa* ICU versus non-ICU isolates are provided in Figures 1 and 2 as this was the only organism with significant spread of carbapenem MICs to value a visual comparison.

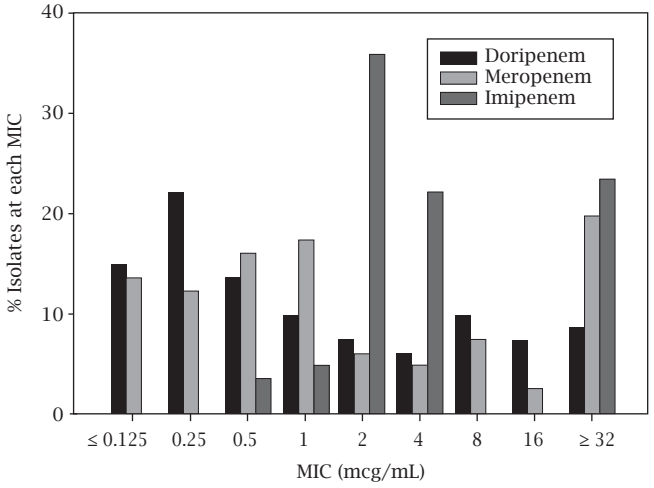

Figure 1: Carbapenem MIC distributions against *P. aeruginosa* collected from the ICU. Detailed MIC distributions for each carbapenem against *P. aeruginosa* isolates. This was the only organism with significant spread of carbapenem MICs to value a visual comparison.

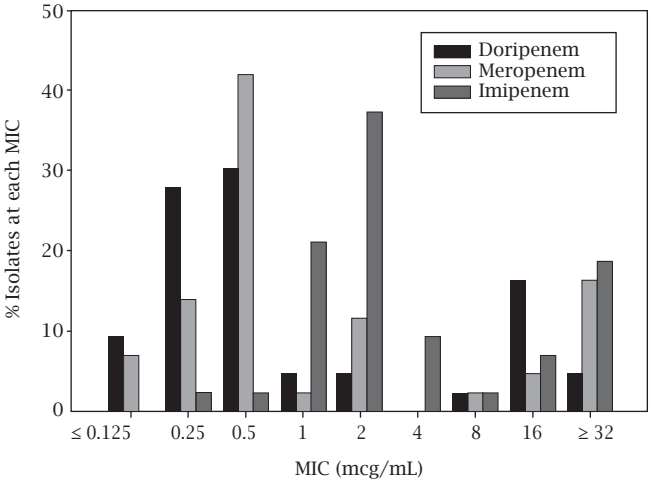

Figure 2: Carbapenem MIC distributions against *P. aeruginosa* collected from outside the ICU. Detailed MIC distributions for each carbapenem against *P. aeruginosa* isolates. This was the only organism with significant spread of carbapenem MICs to value a visual comparison.

RESULTS

The summary of CFR for all carbapenem regimens against the total isolate populations are presented in Table 3. All carbapenem regimens obtained optimal exposures against *E. coli*. For the *K. pneumoniae* isolates, all doripenem and meropenem regimens except regimens of doripenem 500 mg q8h (1-hour infusion) and meropenem 500 mg q8h (0.5-hour infusion) exceeded the CFR target value of 90%. In contrast, the only imipenem regimens to achieve this target were the prolonged infusion regimens of 500 mg q6h or 1,000 mg q8h. Against *P. aeruginosa*, imipenem or meropenem did not achieved 90% CFR with any regimen. While a doripenem regimen of 1,000 mg q8h (over 4h) approached (87%) the target CFR, only a prolonged infusion of 2000 mg q8h (over 4h) exceeded the 90% CFR threshold. Due to very high MICs, no regimens for any of the drugs tested obtained optimal CFR against *A. baumannii*. CFR results for ICU versus non-ICU isolates are presented in Table 4 for *P. aeruginosa* and *K. pneumoniae*. There were no differences in CFR between ICU and non-ICU isolates for any of the carbapenem regimens against *E. coli*; there were too few isolates outside of the ICU for *A. baumannii* to perform the analyses.

Among *P. aeruginosa* isolates collected in the ICU compared with outside the ICU, there were slight differences (approximately 5-10%) in CFR among all the drug regimens in favor of non-ICU isolates. Again, only doripenem 2,000 mg q8h prolonged infusion regimens achieved optimal CFR for both populations. In contrast, CFR for *K. pneumoniae* were greater inside the ICU versus outside the ICU by approximately 10-15% depending on dosing regimen simulated.

For these *K. pneumoniae*, all doripenem and meropenem regimens performed well inside the ICU; however, outside the ICU, only higher doses of doripenem or prolonged infusions, as well as meropenem 2,000 mg q8h (3-hour infusion) achieved optimal CFR. Those differences may be explained by the fact that in the ICU non-susceptibility rates to carbapenems (MIC ≥ 2 μg/mL)

***Table 3. Comparison of the cumulative fraction of response for standard carbapenem regimens against* E. coli, K. pneumoniae, P. aeruginosa, *and* A. baumannii**

Antibiotic regimen (infusion duration)	Cumulative fraction of response (%)			
	E. coli	*K. pneumoniae*	*P. aeruginosa*	*A. baumannii*
Doripenem				
500 mg q8h (1 hr)	95.9	88.9	70.2	42.2
1,000 mg q8h (1 hr)	97.8	92.2	78.5	48.9
2,000 mg q8h (1 hr)	98.7	94.9	85.4	64.6
500 mg q8h (4 hr)	99.9	94.0	79.5	44.7
1,000 mg q8h (4 hr)	100	95.8	87.2	53.0
2,000 mg q8h (4 hr)	100	97.9	93.3	75.0
Imipenem				
500 mg q8h (0.5 hr)	89.9	79.0	46.5	40.4
500 mg q6h (0.5 hr)	95.4	85.3	57.4	42.5
1,000 mg q8h (0.5 hr)	93.9	84.6	58.5	41.7
500 mg q8h (3 hr)	99.5	89.4	65.4	44.1
500 mg q6h (3 hr)	99.9	91.1	69.5	44.1
1,000 mg q8h (3 hr)	100	92.5	71.8	44.2
Meropenem				
500 mg q8h (0.5 hr)	98.5	89.1	66.1	42.4
500 mg q6h (0.5 hr)	99.2	90.8	70.0	43.4
1,000 mg q8h (0.5 hr)	99.4	91.7	72.2	43.8
2,000 mg q8h (0.5 hr)	99.7	93.4	77.8	48.7
500 mg q8h (3 hr)	99.8	91.7	72.7	44.2
1,000 mg q8h (3 hr)	100	93.5	77.6	45.7
2,000 mg q8h (3 hr)	100	95.1	83.0	56.4

Table 4. Comparison of the cumulative fraction of response for standard carbapenem regimens against **P. aeruginosa** *and* **K. pneumoniae** *collected from the ICU compared with those collected outside the ICU*

Antibiotic regimen (infusion duration)	Cumulative fraction of response (%)			
	P. aeruginosa		*K. pneumoniae*	
	ICU (n = 81)	Non-ICU (n = 43)	ICU (n = 86)	Non-ICU (n = 77)
Doripenem				
500 mg q8h (1 hr)	69.2	72.1	92.7	84.7
1,000 mg q8h (1 hr)	77.6	80.2	95.2	88.8
2,000 mg q8h (1 hr)	84.6	86.9	96.9	92.6
500 mg q8h (4 hr)	79.2	80.1	97.3	90.4
1,000 mg q8h (4 hr)	86.9	87.7	97.9	93.5
2,000 mg q8h (4 hr)	92.9	94.1	98.9	96.8
Imipenem				
500 mg q8h (0.5 hr)	43.0	53.0	84.4	72.8
500 mg q6h (0.5 hr)	54.6	62.7	90.7	79.2
1,000 mg q8h (0.5 hr)	56.2	62.8	89.6	79.0
500 mg q8h (3 hr)	62.7	70.3	95.1	83.0
500 mg q6h (3 hr)	67.7	72.9	96.3	85.3
1,000 mg q8h (3 hr)	70.2	74.7	97.2	87.3
Meropenem				
500 mg q8h (0.5 hr)	63.4	71.1	95.5	82.1
500 mg q6h (0.5 hr)	63.4	71.1	95.5	82.1
1,000 mg q8h (0.5 hr)	70.3	75.7	97.4	85.2
2,000 mg q8h (0.5 hr)	76.5	80.3	98.3	88.0
500 mg q8h (3 hr)	70.5	77.0	97.8	84.9
1,000 mg q8h (3 hr)	76.4	79.8	98.7	87.7
2,000 mg q8h (3 hr)	81.9	85.0	99.1	90.7

were lower than in the non-ICU setting (5,8% vs. 20,8% for doripenem [p = 0.02]; 7% vs. 20.8% for meropenem [p = 0.04]; and 14% vs. 24.7% for imipenem [p = 0.13]). Differences in resistance rates were more notorious among isolates from patients with intra-abdominal infection but non-statistically significant differences were obtained due to the small sample size (0% vs. 39.1% for doripenem, meropenem and imipenem [p = 0.30]). This is the first time that such disparities in susceptibility rates have been reported in Colombia deserving further studies.

CFRs were also calculated against all pathogens when separated by source of infection: bloodstream, intra-abdominal, and nosocomial pneumonia (data not shown). Isolates numbers were too small to provide distinctions among source for *A. baumannii* and *E. coli*. For *P. aeruginosa*, CFR was approximately 20% lower for isolates collected in the respiratory tract compared with bloodstream or intra-abdominal for imipenem and meropenem. Although a similar observation was noted for doripenem, the magnitude of the differences were lower (approximately 10%), and only doripenem 2,000 mg q8h (4-hour infusion) again achieved greater than 90% CFR against respiratory *P. aeruginosa*. For *K. pneumoniae* isolates, CFR results were highest against bloodstream and respiratory tract isolates for all antibiotics. In fact, all doripenem and meropenem regimens achieved greater than 90% CFR against bloodstream and respiratory isolates of *K. pneumoniae*. CFR against the 29 intra-abdominal isolates, however, were 10-20% lower for all antibiotics, suggesting the majority of the resistant phenotype is coming from this source.

DISCUSSION

The results of these pharmacodynamic analyses are supported by the high resistance rates among this Colombia collection of *P. aeruginosa* and *A. baumannii*, and likewise the very low resistance rates of the Enterobacteriaceae. While the carbapenems appear to retain very good potency against

this population of Enterobacteriaceae, a concerning phenotype is the *K. pneumoniae* with higher carbapenem MICs that were most apparent from intra-abdominal cultures obtained outside of the ICU. Therefore for empiric treatment of *K. pneumoniae* in this setting, carbapenem dosages above that currently approved may be required. This finding deserves further studies as KPC carbapenemases have been reported previously and might very well be the cause of this resistance.[7] Standard (approved) dosing regimens of doripenem (500 mg q8h as a 1-hour infusion), meropenem (500 mg or 1,000 mg q8h as 0.5-hour infusion and 500 mg q6h as a 0.5-hour infusion), and imipenem (500 mg or 1,000 mg q8h as 0.5 hour infusion) all achieved optimal CFR against *E. coli* isolates, regardless of collection in or outside of the ICU.

Against *A. baumannii*, none of the carbapenems achieved optimal CFR. More importantly, the very high MICs for isolates in this region also compromise the ability for higher doses combined with prolonged infusions to significantly improve CFR. The highest CFR against this population of 34 *A. baumannii* was obtained by doripenem 2,000 mg q8h as a 4-hour infusion (75.0%). Combination therapy or selection of other antimicrobials with unique mechanisms of action appears to be required to addressing this high level of *A. baumannii* resistance among ICU isolates. Characterization of the mechanism of resistance of these isolates deserves further studies as OXA-23 carbapenemases have also been reported by our group previously and may explain the high level resistance to carbapenems.[8] The majority of isolates collected during COMPACT-COLOMBIA were from the ICU, so conclusions about treatment of *A. baumannii* outside of the ICU cannot be made.

Notably, CFR gains by using higher doses and prolonged infusions were observed most frequently against the *P. aeruginosa* population. Standard (approved) doses for doripenem and meropenem achieved CFRs of 70.2% to 72.2%, while imipenem CFRs were lower than 60%. The use of higher doses combined with prolonged infusions (unapproved dosing regimens) improved CFR to 93.3% for doripenem 2,000 mg q8h (4-hour infusion) and up to 83% for meropenem 2,000 mg q8h (3-hour infusion). Although prolonged infusions improved CFR for imipenem, the inability to administer doses higher than 1,000 mg hindered significant improvements against *P. aeruginosa*. Even 1,000 mg q8h (3-hour infusion) only achieved 71.8% CFR. The differences between ICU and non-ICU isolates were noted among *P. aeruginosa* as well. As is apparent in Figures 1 and 2, the MIC distribution curve is shifted to the right for the ICU isolates, thus leading to CFR results that are on average 5% to 10% lower for all carbapenems compared with isolates outside the ICU. These data suggest that higher dosing, prolonged infusion doripenem or meropenem regimens may be suitable for empirically covering ICU *P. aeruginosa*.

Although the *in vitro* assessment of potency can be an important determinant of clinical outcome, the PD profiling undertaken in this study provides additional insight as to the clinical viability of these carbapenems by altering the dose, dosing interval and/or administration technique to overcome phenotypic variations in an adult population with conserved renal function as defined herein. It should be remembered that additional dosage alterations may be required in adult patients with substantially reduced renal function and that the simulations provided are not intended to be used for special populations (i.e., pediatric patients) excluded from the current analysis. Moreover, it is necessary to emphasize that this article utilizes Monte Carlo simulation as a predictive tool for clinical success; in clinical practice other factors such as host competence and use of combination therapies may generate differing outcomes.

Lastly, while the breakpoints for many antibiotics, including the carbapenems, are being reduced in an attempt to provide more concordance with clinical success, this will result in a higher proportion of non-susceptible organisms and inadvertent drive clinicians away from pharmacodynamically sound regimens. Thus, a full understanding of the PD characteristics of these therapeutic entities is paramount if clinical success is to be maintained in the wake of phenotypic change.

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