Pharmacokinetic/pharmacodynamic evaluation of the efficacy and cost-effectiveness of various carbapenem dosing regimens for the treatment of Gram-negative bacterial bloodstream infections

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Introduction

In the climate of multidrug-resistance, carbapenems are often initiated empirically in critically patients with bloodstream infections (BSI). However, conventional carbapenem dosing regimens (CDRs) are often sub-optimal in critically-ill patients, whereby pathophysiological changes may result in pharmacokinetic alterations. Our study aimed to compare the expected population probability of target attainment and identify the most cost-effective CDR against Gram-negative bacteria (GNB) isolated from BSI in our institution.

Methods

Non-repeat GNB BSI isolates from a local 1700-bed academic hospital from Jan-Jun 2013 were collected. MIC testing for imipenem (IMI), meropenem (MER), doripenem (DOR) was performed using CLSI broth micro-dilution to determine overall susceptibility rates.

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Monte Carlo simulations were used to generate the steady-state pharmacokinetic profiles of 5,000 subjects for the various CDRs, using pharmacokinetic parameters from published studies conducted in critically-ill population.[1-3]

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The respective CDRs' cumulative fraction of response (CFR) was tabulated as the proportion of the simulated population achieving *f*%T>MIC of 40% (PK/PD parameter which best predicts carbapenem efficacy *in vivo*), taking into account the MIC distribution of the collected isolates.

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Carbapenem costs were based on pharmacy acquisition cost. Cost-effectiveness was calculated as: total daily drug cost / CFR.[4]

Results

A total of 602 GNB isolates were collected (Table 1). The susceptibilities of the isolates to IMI, MER and DOR are shown in Table 2.

Organism	*No. of isolates*	*% of isolates*
Acinetobacter baumannii	66	11.0%
Escherichia coli	100	16.6%
Enterobacter sp.	62	10.3%
Klebsiella sp.	271	45.0%
Pseudomonas aeruginosa	100	16.6%
Others	3	0.5%
Total	602	100.0%

Table 1: Breakdown of 602 GNB BSI

(A) Pseudomonas aeruginosa

	CLSI susceptibilities (% of isolates)		
Carbapenem	*S (≤2)*	*I (4)*	*R (≥8)*
Imipenem	36.0%	20.0%	44.0%
Meropenem	61.0%	7.0%	32.0%
Doripenem	62.0%	8.0%	30.0%

(B) Enterobacteriaceae

	CLSI susceptibilities (% of isolates)		
Carbapenem	*S (≤1)*	*I (2)*	*R (≥4)*
Imipenem	87.4%	10.3%	2.3%
Meropenem	96.8%	1.1%	2.1%
Doripenem	95.9%	1.1%	3.0%

(C) Acinetobacter baumannii

	CLSI susceptibilities (% of isolates)		
Carbapenem	*S (≤2)*	*I (4)*	*R (≥8)*
Imipenem	42.4%	0.0%	57.6%
Meropenem	40.9%	0.0%	59.1%
Doripenem	40.9%	1.5%	57.6%

Table 2: Susceptibilities of A) *P. aeruginosa*, (B) Enterobacteriaceae & (C) *A. baumannii* to IMI, MER and DOR

3A

Carbapenem / Dosage interval (Infusion time)	CFR	Cost / %CFR
Imipenem 0.5g q 8hr (0.5-hr infusion)	41%	$1.56
Imipenem 0.5g q 8hr (3-hr infusion)	61%	$1.05
Imipenem 1g q 8hr (0.5-hr infusion)	54%	$2.38
Imipenem 1g q 8hr (3-hr infusion)	71%	$1.80
Meropenem 1g q 8hr (0.5-hr infusion)	66%	$0.83
Meropenem 1g q 8hr (3-hr infusion)	75%	$0.73
Meropenem 2g q 8hr (0.5-hr infusion)	71%	$1.53
Meropenem 2g q 8hr (3-hr infusion)	83%	$1.31
Doripenem 0.5g q 8hr (0.5-hr infusion)	67%	$2.84
Doripenem 0.5g q 8hr (4-hr infusion)	75%	$2.53
Doripenem 1g q 8hr (0.5-hr infusion)	73%	$5.20
Doripenem 1g q 8hr (4-hr infusion)	83%	$4.58

3B

Imipenem 0.5g q 8hr (0.5-hr infusion)	86%	$0.74
Imipenem 0.5g q 8hr (3-hr infusion)	98%	$0.65
Imipenem 1g q 8hr (0.5-hr infusion)	89%	$1.43
Imipenem 1g q 8hr (3-hr infusion)	99%	$1.29
Meropenem 1g q 8hr (0.5-hr infusion)	98%	$0.55
Meropenem 1g q 8hr (3-hr infusion)	99%	$0.55
Meropenem 2g q 8hr (0.5-hr infusion)	99%	$1.10
Meropenem 2g q 8hr (3-hr infusion)	99%	$1.10
Doripenem 0.5g q 8hr (0.5-hr infusion)	98%	$1.94
Doripenem 0.5g q 8hr (4-hr infusion)	99%	$1.92
Doripenem 1g q 8hr (0.5-hr infusion)	99%	$3.84
Doripenem 1g q 8hr (4-hr infusion)	99%	$3.83

Cost expressed in Singapore dollars. (1€ ≈ SGD1.70)

3C

Carbapenem / Dosage interval (Infusion time)	CFR	Cost / %CFR
Imipenem 0.5g q 8hr (0.5-hr infusion)	37%	$1.72
Imipenem 0.5g q 8hr (3-hr infusion)	42%	$1.51
Imipenem 1g q 8hr (0.5-hr infusion)	39%	$3.31
Imipenem 1g q 8hr (3-hr infusion)	43%	$2.95
Meropenem 1g q 8hr (0.5-hr infusion)	40%	$1.35
Meropenem 1g q 8hr (3-hr infusion)	44%	$1.25
Meropenem 2g q 8hr (0.5-hr infusion)	42%	$2.59
Meropenem 2g q 8hr (3-hr infusion)	49%	$2.23
Doripenem 0.5g q 8hr (0.5-hr infusion)	42%	$4.54
Doripenem 0.5g q 8hr (4-hr infusion)	42%	$4.48
Doripenem 1g q 8hr (0.5-hr infusion)	42%	$8.96
Doripenem 1g q 8hr (4-hr infusion)	42%	$8.96

Table 3.CFR & cost-effectiveness of various carbapenem dosing regimens against (A) *P. aeruginosa*, (B) Enterobacteriaceae & (C) *A. baumannii*

Conclusions

Our study suggested that meropenem 1-2g q 8h over 3-hr is the most optimal and cost-effective dosage regimen recommended for empiric treatment of GNB BSI in our institution. In addition, conventional CDRs may not be optimal in a hospital with microorganisms with reduced susceptibilities to carbapenems, especially in the critically-ill population.. As none of the CDRs were optimal against AB, polymyxins in combination with other antibiotics may have to be considered as empiric therapy in suspected AB bacteraemia in our institution. Moving forward, this pharmacoeconomic tool can be employed to assess the cost-effectiveness of any anti-infectives, for inclusion into our hospital formulary according to our local epidemiological patterns.

References
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