eP004
ePoster Viewing
PK/PD to improve treatment of critically ill patients

PHARMACOKINETIC/PHARMACODYNAMIC EVALUATION OF THE EFFICACY AND COST-EFFECTIVENESS OF VARIOUS CARBAPENEM DOSING REGIMENS FOR THE TREATMENT OF GRAM-NEGATIVE BACTERIA BLOODSTREAM INFECTIONS

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Objective: In the climate of multidrug-resistance, carbapenems are often initiated empirically in 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. The 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 January - June 2013 were collected. MIC testing for imipenem (IMI), meropenem (MER), doripenem (DOR) was performed using CLSI broth microdilution technique to determine MIC_{50}, MIC_{90} and overall susceptibility rates. 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. The respective CDRs' cumulative fraction of response (CFR) was tabulated as the proportion of the simulated population achieving 40% $f_{T>MIC}$ (PK/PD parameter which best predicts carbapenem efficacy *in vivo*), taking into account the MIC distribution. Carbapenem costs were based on pharmacy acquisition cost. Cost-effectiveness was calculated as: total daily drug cost / CFR.

Results: 602 GNB BSI isolates were collected - 66 *Acinetobacter baumannii* (AB), 100 *Pseudomonas aeruginosa* (PA) and 436 *Enterobacteriaceae* (EB) (63% *Klebsiella pneumoniae* and 23% *Escherichia coli*). MIC_{50}/MIC_{90} (mg/L) of IMI, MER and DOR were 32/>=64, >=64/>=64 and 32/>=64, respectively for AB. MIC_{50}/MIC_{90} (mg/L) of IMI, MER and DOR were 4/>=64, 1/>=64 and 2/>=64, respectively for PA. MIC_{50}/MIC_{90} (mg/L) of IMI, MER and DOR were 0.5/2, <=0.25/<=0.25 and <=0.25/<=0.25, respectively for EB. The CFR and cost-effectiveness for various CDR are shown in Table 1. None of the CDR achieved an optimal CFR (>90%) against AB (CFR = 42-49%) while meropenem 2g q8h over 3h and doripenem 1g q8h over 4h are able to achieve a near optimal CFR (83%) against PA with DOR being the most cost-effective regimen. Against EB, IMI, MER and DOR were able to achieve optimal CFR (98%) with meropenem 1g q8h over 3h being the most cost-effective.

Conclusion: This study shows that conventional CDRs may not be effective in a hospital with microorganisms with reduced susceptibilities to carbapenems, especially in the critically-ill population. Our study suggested that meropenem 2g q8h over 3h is the optimal and cost-effective dosage regimen recommended for empiric treatment of GNB BSI in our institution. As none of the CDRs were optimal against AB, meropenem 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.

Table 1.Cumulative fraction of response and cost-effectiveness of imipenem, meropenem & doripenem

Organism	Carbapenem / Dosage interval (Infusion time)	Total Daily Drug Cost	CFR	Cost / %CFR
Acinetobacter baumannii	Imipenem 0.5g q 8hr (0.5-hr infusion)	$64	37%	$1.72
	Imipenem 0.5g q 8hr (3-hr infusion)	$128	42%	$1.51
	Imipenem 1g q 8hr (0.5-hr infusion)	$64	39%	$3.31
	Imipenem 1g q 8hr (3-hr infusion)	$128	43%	$2.95
	Meropenem 1g q 8hr (0.5-hr infusion)	$55	40%	$1.35
	Meropenem 1g q 8hr (3-hr infusion)	$110	44%	$1.25
	Meropenem 2g q 8hr (0.5-hr infusion)	$55	42%	$1.29
	Meropenem 2g q 8hr (3-hr infusion)	$110	49%	$1.11
	Doripenem 0.5g q 8hr (0.5-hr infusion)	$190	42%	$4.54
	Doripenem 0.5g q 8hr (4-hr infusion)	$380	42%	$4.48
	Doripenem 1g q 8hr (0.5-hr infusion)	$190	42%	$8.98
	Doripenem 1g q 8hr (4-hr infusion)	$380	42%	$8.98
Pseudomonas aeruginosa	Imipenem 0.5g q 8hr (0.5-hr infusion)	$64	41%	$1.56
	Imipenem 0.5g q 8hr (3-hr infusion)	$128	61%	$1.05
	Imipenem 1g q 8hr (0.5-hr infusion)	$64	54%	$2.38
	Imipenem 1g q 8hr (3-hr infusion)	$128	71%	$1.80
	Meropenem 1g q 8hr (0.5-hr infusion)	$55	66%	$0.83
	Meropenem 1g q 8hr (3-hr infusion)	$110	75%	$0.73
	Meropenem 2g q 8hr (0.5-hr infusion)	$55	71%	$0.78
	Meropenem 2g q 8hr (3-hr infusion)	$110	83%	$0.65
	Doripenem 0.5g q 8hr (0.5-hr infusion)	$190	67%	$2.84
	Doripenem 0.5g q 8hr (4-hr infusion)	$380	75%	$2.53
	Doripenem 1g q 8hr (0.5-hr infusion)	$190	73%	$5.20
	Doripenem 1g q 8hr (4-hr infusion)	$380	83%	$4.58
Enterobacteriaceae	Imipenem 0.5g q 8hr (0.5-hr infusion)	$64	86%	$0.74
	Imipenem 0.5g q 8hr (3-hr infusion)	$128	98%	$0.65
	Imipenem 1g q 8hr (0.5-hr infusion)	$64	89%	$1.43
	Imipenem 1g q 8hr (3-hr infusion)	$128	99%	$1.29
	Meropenem 1g q 8hr (0.5-hr infusion)	$55	98%	$0.55
	Meropenem 1g q 8hr (3-hr infusion)	$110	99%	$0.55
	Meropenem 2g q 8hr (0.5-hr infusion)	$55	99%	$0.55
	Meropenem 2g q 8hr (3-hr infusion)	$110	99%	$0.55
	Doripenem 0.5g q 8hr (0.5-hr infusion)	$190	98%	$1.94
	Doripenem 0.5g q 8hr (4-hr infusion)	$380	99%	$1.92
	Doripenem 1g q 8hr (0.5-hr infusion)	$190	99%	$3.84
	Doripenem 1g q 8hr (4-hr infusion)	$380	99%	$3.83

MIC= minimum inhibitory concentration, CFR= cumulative fraction of response,

Total daily drug cost expressed in Singapore dollars.

* The most optimal and cost-effective dosing regimens evaluated for each organism type.