29th ECCMID Amsterdam, Netherlands 13 – 16 April 2019

The congress of ESCMID

P1966 Exploring piperacillin pharmacokinetics in non-critically ill patients with bloodstream infections due to *Enterobacteriaceae*

Vicente Merino Bohórquez[1], Fernando Docobo Perez*[2], Adoracion Valiente Mendez[1], Mercedes Delgado-Valverde[1], Manuel Cameán[1], William Hope[3], Alvaro Pascual Hernandez[1], Jesús Rodríguez-Baño[1]

[1] Hospital Universitario Virgen Macarena, Sevilla, Spain, [2] Universidad de Sevilla Facultad de Medicina, Sevilla, Spain, [3] University of Liverpool, Liverpool, United Kingdom

Background: This study analyzes the pharmacokinetic variability of piperacillin in non-critically ill patients with Enterobacteriaceae bloodstream infections (EBSI) and explores predicted clinical outcomes and piperacillin-related neurotoxicity in these patients.

Materials/methods: Hospitalized, non-critically ill patients treated with piperacillin-tazobactam for EBSL were included. Four serum samples per patient were collected and analyzed. Two different piperacillin-tazobactam regimens: (a) 4/0.5g (4h infusion) q8h, and (b) first dose 4/0.5g (30 minutes infusion) followed by 4/0.5g (4h infusion) starting immediately after the first dose. A population pharmacokinetic model was developed using the Pmetrics package for R. Monte Carlo simulations (n=2000) of various dosage regimens of 4g piperacillin, administered q8h by short (0.5 h) or long (4 h) infusion or with a loading dose were performed to determine the probability of target attainment (PTA) using $fT_{>MIC}$ of 50% and 100% for efficacy, and targets for piperacillin-associated neurotoxicity (serum concentration threshold of 157.2 mg/L [Quinton et al. AAC 2017] or Cmin >361.4 mg/L [Imani et al. JAC 2017]).

Results: Twenty-eight patients (102 samples) were included. Extended piperacillin infusions reached a PTA>90% (50% $fT_{>MIC}$) within in the susceptibility range, although a loading dose did not greatly improve the expected outcome. None of the simulated dosages attained the pharmacodynamic target $fT_{>MIC}$ for 100% of the dosing interval. Only the simulation of 4g piperacillin administered q8h by short (0.5 h) infusion showed a low (<2%) rate of piperacillin neurotoxicity.

Conclusions: The study supports the use of extended infusions of piperacillin in non-critically ill patients with EBSL. The benefits of a loading dose are not clear in this patient population. The risk of piperacillin associated neurotoxicity was low.

Table 1. Probability of target attainment using a $fTMIC_{0\text{-}24h}$ =50% or 100% as pharmacodynamic target after simulation: Dosage 1, 4g (0.5 h infusion); Dosage 2, 4g (4 h infusion); Dosage 3, first dose [4g (0.5 h infusion) + 4g (4 h infusion)] followed by 4g (4 h infusion) q8h.

	fT_{MIC}=50%			fT_{MIC}=100%		
	Dosage			Dosage		
MIC	1	2	3	1	2	3
0.06	91.95	100	100	79.75	88.7	88.3
0.125	90.95	100	100	76.95	87.25	86.4
0.25	89.9	100	100	73.35	85.05	84.05
0.5	88.6	100	100	68	81.85	81.35
1	86.85	100	100	62.5	77.25	77.7
2	83.65	100	100	54.6	68.8	71.5
4	78.15	100	100	42.7	29.4	61.95
8 EUCAST (S)	68.65	100	100	25.4	2.45	44.1
16 EUCAST (I)	46.7	93.55	98.75	4.05	0.2	13
32 (EUCAST R)	15.05	29.65	50.55	0.25	0	0.65
64	1.75	3.15	7.9	0	0	0
128	0.05	0.25	0.65	0	0	0
256	0	0	0.05	0	0	0