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Paper Poster Session
PK/PD of agents against Gram-negatives

Development of a pharmacokinetic model for piperacillin-tazobactam in non-critically ill patients with bloodstream infection due to Enterobacteriaceae

Adoracion Valiente Mendez*[1], Vicente Merino Bohórquez[2], Manuel Cameán[2], Mercedes Delgado[3], Alvaro Pascual Hernandez[4], William W. Hope[5], Jesús Rodríguez-Baño[6]

[1]*Ugc Intercentros de Enfermedades Infecciosas, Microbiología Y Medicina Preventiva, Hospitales Universitarios Virgen Macarena Y Virgen del Rocío, Sevilla, Spain*

[2]*Ugc de Farmacia, Hospital Universitario Virgen Macarena, Seville, Spain*

[3]*Hospital Universitario Virgen Macarena, Ugc Intercentros de Enfermedades Infecciosas, Microbiología Y Medicina Preventiva, Hospitales Universitarios Virgen Macarena Y Virgen del Rocío, Seville, Spain*

[4]*University Hospital Virgen Macarena, Infectious Diseases and Clinical Microbiology Unit, Sevilla, Spain*

[5]*Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, United Kingdom, United Kingdom*

[6]*Hospital Universitario Virgen Macarena Y Virgen del Rocío, Universidad de Sevilla, Enfermedades Infecciosas, Microbiología Y Medicina Preventiva, Seville, Spain*

Background: There is sparse data that relates to the variability in serum concentrations of piperacillin/tazobactam (PTZ) in non-critically ill patients with bacteraemia. Our objectives were to describe the variability of piperacillin free serum concentrations and develop a pharmacokinetic model in non-critically ill patients with bloodstream infections due to *Enterobacteriaceae* (BSI-E), exploring the determinants likely to achieve adequate concentrations in relation to any value of minimum inhibitory concentration (MIC).

Methods: A prospective cohort study of adult patients with BSI-E receiving empirical monotherapy with PTZ administered at 4/0.5 g tid in extended infusion (EI) over 4 hours using an infusion pump. Demographic, epidemiological and clinical data were collected. Serum concentrations of piperacillin were measured at steady state on day 2 of therapy at 1, 4, 6 and 8 hours (h) after the infusion using high performance liquid chromatography. Susceptibility testing was performed by microdilution using EUCAST recommendations (susceptible, MIC≤8 mg/L; resistant >16). The nonparametric adaptive grid (NPAG) algorithm, provided within the Pmetrics® software package, was used to construct and fit a population pharmacokinetic model. The probability of achieving the targeted pharmacokinetic-pharmacodynamic parameter (40%*f*T>MIC) was studied using Monte Carlo simulations.

Results: We included 24 patients; their median aged was 75.5 (range, 48-85); *E. coli* was the most frequent pathogen (54%). The median serum concentrations of piperacillin (range) were: 1st h, 49.18 mg/L (13.7-106.5); 4th h, 85.5 (20.7-136.9); 6th h, 51.8 (7.8-155.6); and 8th h 26.7 (1.5-106.8). MIC was ≥16 mg/L only in one patient (4.1%). The only variable associated to clearance of piperacillin was creatinine clearance by multivariate linear regression (adjusted R^2 =0.89). Monte Carlo simulation showed a >90% probability to achieve 40% *f*T>MIC with the regimen with an initial bolus dose (4 g

over 30 min) followed by 4 g tid in extended infusion (EI) for MIC values up to 16 mg/L (figure). All patients were cured.

Conclusions: A high variability in piperacillin free serum concentrations was observed in this population; concentrations correlated with creatinine clearance. Optimised dosing would provide a high probability of target achievement for intermediate susceptible isolates.

Figure. Probability to achieve (PTA) 40%*f*T>MIC with different piperacillin-tazobactam intravenous regimens related to minimum inhibitory concentration (MIC) value (mg/L).