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Pharmacokinetics of piperacillin in patients with haematological malignancies: population analysis and Monte Carlo simulation of short versus prolonged infusion

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Background: Piperacillin administered in combination with tazobactam is widely used in haematological malignancy setting. The objective of this study was to perform population PK analysis of piperacillin PK data in this population and to investigate optimal dosing regimens in relation with minimal inhibitory concentration (MIC) distribution of all gram-negative blood stream infections (BSI) over the study period.

Material/methods: This was a single-centre prospective study including adult haematological malignancy patients receiving piperacillin/tazobactam as a short (30min, n=14) or prolonged (≥ 4h, n=23) infusion over a 10-month period (July 2015 to May 2016). Were monitored: *(i)* antibiotic peak and trough concentrations measured by HPLC at least 24h after infusion initiation, *(ii)* renal and hepatic functions, *(iii)* serum proteins and albumin, *(iv)* polymorphonuclear neutrophil counts (PMNs). Data were analysed with a nonparametric population approach using the R package Pmetrics. Then, 1000-patient Monte Carlo simulations were performed based on the final model to investigate the influence of infusion duration (30min *versus* 4h), and renal function on the probability of target attainment (PTA). The efficacy target was defined as the percentage of time during which piperacillin free plasma concentration was above the MIC (fT>MIC) of either 50% or 90%. The MIC distribution of all gram-negative BSI over the study period was retrospectively determined by liquid turbidity method and used as a reference.

Results: Thirty-seven patients were included (20 males, 17 females) with 31 (84%) having febrile neutropenia (PMNs< 1G/L) and 6 (16%) having fever with a normal PMNs. Mean (±SD) age, weight, PMNs and creatinine clearance according to Cockcroft-Gault Equation (CCR) were of 49 ± 16 years, 69±14 kg, 0,3±0,2 and 102±36 mL/min, respectively. The median MIC value of all gram-negative BSI (n=48) was 8 mg/L. Fourteen (35,5%) patients received short-time infusion and 23 (64,5%) a prolonged one. Data were best described by a one compartment model, with covariates CCR and bilirubine influencing piperacillin clearance (CL), and gender influencing volume of distribution (V). Both population and individual predictions correlated well with observed concentrations (R-squared = 0.77 and 1, respectively), with little mean prediction error (-6.3 and -0.22 mg/L) and root mean squared error (27.6 and 1.4 mg/L). Simulations showed that prolonged infusion and renal impairment were associated with increased in fT>MIC and higher PTA. For a reference MIC value of 8 mg/L, a 30 min infusion of 4g administered every 8h in female patients achieved mean values of fT>MIC of 47%, 60%, and 70% in patients with CCR of 120, 60, and 30 mL/min, respectively. The corresponding values for a 4h infusion were 75%, 84%, and 89%, respectively.

Conclusions: Prolonged infusion of piperacillin/tazobactam optimizes the PK/PD of piperacillin in haematological malignancy patients with febrile neutropenia.