27th ECCMID Vienna, Austria 22 – 25 April 2017

The congress of ESCMID

Session: EV023 Pharmacoepidemiology, improved prescribing and antibiotic stewardship

Category: 5b. Pharmacokinetics/pharmacodynamics of antibacterial drugs & therapeutic drug monitoring

22 April 2017, 08:45 - 15:30
EV0447

Pharmacokinetic/pharmacodynamic parameters and clinical outcomes in patients treated with extended infusion cefepime or piperacillin/tazobactam with augmented renal clearance and Pseudomonas aeruginosa infections using E-test MICs

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Background: Maximizing pharmacokinetic/pharmacodynamic (PK/PD) parameters is necessary to optimize outcomes in patients with Pseudomonas aeruginosa (PSa) infections. Augmented renal clearance (ARC) is one of many factors that may alter PK/PD, and is associated with subtherapeutic β-lactam concentrations. Use of extended infusion cefepime (CEF) and piperacillin/tazobactam (P/T) has been suggested to maximize fT>MIC in those with ARC. We sought to correlate PK/PD predictions of antibacterial efficacy and clinical outcomes in patients with PSa bacteremia or pneumonia treated with extended infusion CEF or P/T.

Material/methods: Retrospective single-center study of hospitalized patients with PSa bacteremia or pneumonia from 1/2013 to 9/2016. CEF (2g every 8 hours) and P/T (4.5g every 8 hours) were administered over 4 hours after a loading dose infused over 30 minutes and MIC was determined by E-test. Published population PK evaluations in critically ill patients were used and PD analyses were conducted using calculated patient-specific PK parameters and known MIC values for PSa. Concentration-time profiles were generated every 6 minutes using first-dose drug exposure estimates including a loading infusion. Clinical cure was defined as resolution of signs and symptoms attributable

to PSa infection without need for escalation of antimicrobial. Nominal data is presented a percentage, continuous parametric data as mean ± standard deviation, and continuous non-parametric data as median [25-75% interquartile range]. Two-tailed X2, Fisher's exact, student's t-test or Mann-Whitney U-test were performed as appropriate, and a p-value <0.05 was considered statistically significant.

Results: Seventy patients were included in the analysis (27 CEF and 43 P/T). Groups had similar age (41.3±13.8 CEF vs 43.7±12.7 years P/T, p=0.47), serum creatinine (0.56±0.21 vs 0.52±0.17 mg/dL, p=0.35) weight (72.1 [59-85.8] vs. 76.2 [56.3-89.8] kg, p=0.74) and creatinine clearance (156.3 [138.6-211.2] vs. 172 [149-201.1] mL/min, p=0.3). The majority required ICU care (59.3% vs. 67.4%, p=0.49), for a median of 16 [11-20] vs. 11.5 [5-21.5] days (p=0.2), and mechanical ventilation (55.6% vs. 51.2%, p=0.81) for a median of 5 [3.5-13] vs. 11 [5.5-16.5] days (p=0.34). While majority of patients had pneumonia (80%), including one in each group with concurrent bacteremia, there were more patients treated for bacteremia in the CEF group (44.4% vs 9.3%, p<0.001). Median MIC was 4 [2-4] mg/L CEF and 8 [4-8] mg/L P/T, p<0.001. The fT>MIC was significantly higher in CEF group (90.7 [72.6-100] vs. 55 [45.7-72.7], p<0.001). Clinical cure was higher in the CEF group (92.6% vs, 72.1%, p=0.037), but mortality (7.4% vs 20.9%, p=0.1) and infection-related mortality (0 vs 4.7%, p=0.46) were similar.

Conclusions: Patients with ARC and PSa pneumonia and/or bacteremia who received extended-infusion CEF achieved higher fT>MIC and clinical cure than those receiving extended infusion PT. Further studies are warranted.