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Poster Session VI
PK/PD of antibiotics against Gram-positives

PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) PROFILE OF ORAL AMOXICILLIN IN ELDERLY PATIENTS WITH GRAM-POSITIVE INFECTIONS REQUIRING PROLONGED ANTIMICROBIAL COURSES.

L. Pagani[1], V. Vitrat[2], C. Janssen[2], F. Jehl[3], A. Renzoni[4], J. Gaillat[2], J.P. Bru[2]

[1]Infect. Dis. Unit, Bolzano Central Hospital, Bolzano, Italy ; [2]Infect. Dis. Unit, CHANGE, Annecy, France ; [3]Lab. Bacteriol., Univ. Hosp. Strasbourg, Strasbourg, France ; [4]Infect. Dis. Unit, HUG, Geneva, Switzerland

Objectives: Amoxicillin still represents a drug of choice for the treatment of streptococcal and drug-susceptible enterococcal infections. Oral amoxicillin (OA) has a very good bioavailability (80%), with a dose-dependent peak level (Cmax) two hours after administration, and a half-life of around one hour. Its PK/PD determinant is free active drug exposure over time (time-dependent activity). Bacterial bone and joints infections or endocarditis require high antimicrobial doses to attain target concentration at the infection site, usually over weeks or months. We investigated the PK/PD profile of OA in patients over 75 years with proven amoxicillin-susceptible Gram-positive infections, to assess the feasibility of an early oral switch therapy for such infections in elderly patients.
Methods: Ten patients (mean age 81.5 years, range 77-88) were treated with OA either 2 g/6h or 2 g/8h, after 10 days of injectable antimicrobial treatment for 5 endocarditis and 5 prosthetic bone infections. Eight were streptococcal infections (3 *S. gallolyticus*, 3 *S. agalactiae*, 1 *S. dysgalactiae*, 1 *Abiotrophia sp.*) and two were due to *E. faecalis*. Amoxicillin minimum inhibitory concentrations (MIC) ranged between 0.06 and 0.25 mg/L. Serum samples were drawn 1 hour after one drug administration and immediately before the next one for determination of Cmax and trough levels (Cmin), respectively. Amoxicillin levels were analysed using high-performance liquid chromatography.
Results: Patients' mean serum creatinine value was 121.3 mg/L (range 76-285, n.v. 53-97). Patients with any kind of renal replacement therapy were excluded. Mean amoxicillin Cmax was 32.9 mg/L (range 11.8-72, SD ± 19) and mean Cmin was 23.4 mg/L (range 7.1-66.2, SD ± 19.5). As expected, Cmin were lower for patients who have been given OA every 8 hours (mean 8.7 mg/L, SD ± 3.12) than for patients who received OA every 6 hours (mean 26.8 mg/L, SD ± 21.2). Cmin were directly correlated to creatinine value, thus indicating a likely prolonged drug half-life in the presence of decreased renal function. No adverse events attributable to either drug regimen were observed.
Conclusion: Targeting therapeutic levels 4-8 folds over MIC at the infection site, OA attained such levels in all cases of infections caused by strains with MIC up to 0.25 mg/L. Indeed, a 100% exposure-time course was observed in our patients with both regimens. Wide inter-individual Cmin variability suggests that OA PK profile and consequent drug disposition may be correlated to age-related variation in renal clearance. Split dosing warrants steadier therapeutic drug level over time, and would probably allow lessening the daily dosage or targeting pathogens with higher MIC. Although very limited in sample size, this on-going study suggests that OA can be a safe and effective option for long-term treatment of infections caused by amoxicillin-susceptible Gram-positive pathogens in elderly patients.