High beta-Lactamase Levels Change the Pharmacodynamics of beta-Lactam Antibiotics in Pseudomonas aeruginosa Biofilms

Resistance to beta-lactam antibiotics is a frequent problem in Pseudomonas aeruginosa lung infection of cystic fibrosis (CF) patients. This resistance is mainly due to the hyperproduction of chromosomally encoded beta-lactamase and biofilm formation. The purpose of this study was to investigate the role of beta-lactamase in the pharmacokinetics (PK) and pharmacodynamics (PD) of ceftazidime and imipenem on P. aeruginosa biofilms. P. aeruginosa PAO1 and its corresponding beta-lactamase-overproducing mutant, PA Delta DDh2Dh3, were used in this study. Biofilms of these two strains in flow chambers, microtiter plates, and on alginate beads were treated with different concentrations of ceftazidime and imipenem. The kinetics of antibiotics on the biofilms was investigated in vitro by time-kill methods. Time-dependent killing of ceftazidime was observed in PAO1 biofilms, but concentration-dependent killing activity of ceftazidime was observed for beta-lactamase-overproducing biofilms of P. aeruginosa in all three models. Ceftazidime showed time-dependent killing on planktonic PAO1 and PA Delta DDh2Dh3. This difference is probably due to the special distribution and accumulation in the biofilm matrix of beta-lactamase, which can hydrolyze the beta-lactam antibiotics. The PK/PD indices of the AUC/MBIC and C-max/MBIC (AUC is the area under concentration-time curve, MBIC is the minimal biofilm-inhibitory concentration, and C-max is the maximum concentration of drug in serum) are probably the best parameters to describe the effect of ceftazidime in beta-lactamase-overproducing P. aeruginosa biofilms. Meanwhile, imipenem showed time-dependent killing on both PAO1 and PA Delta DDh2Dh3 biofilms. An inoculum effect of beta-lactams was found for both planktonic and biofilm P. aeruginosa cells. The inoculum effect of ceftazidime for the beta-lactamase-overproducing mutant PA Delta DDh2Dh3 biofilms was more obvious than for PAO1 biofilms, with a requirement of higher antibiotic concentration and a longer period of treatment.