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ePoster Viewing

Antimicrobials: antimicrobial PK/PD, pharmacogenomics, pharmacoeconomics and general pharmacology, drug interaction studies

Lack of PK/PD target attainment in de-escalated antibiotic therapy in critically ill patients: less is not always more

M. Carlier[1], J. Roberts[2,3,4], V. Stove[1,5], A. Verstraete[1,5], J. Lipman[2,4], J. De Waele[1,5]

[1]*Ghent University, Ghent, Belgium*

[2]*University of Liverpool, Liverpool, Belgium*

[3]*Royal Brisbane and Women's Hospital, Brisbane, Australia*

[4]*Ghent University Hospital, Ghent, Belgium*

Objective: De-escalation of empirical antibiotic therapy is often included in antimicrobial stewardship programs in critically ill patients, but differences in pharmacokinetic/pharmacodynamic (PK/PD) target attainment when switching antibiotics are rarely considered. A recent study found that de-escalation to narrow spectrum antibiotics did not reduce intensive care unit length of stay and actually increased use of antibiotics in patients who had been de-escalated. We hypothesized that PK/PD target attainment after de-escalation may be lower than with empiric therapy. The primary objective of this study was therefore to compare probability to achieve a therapeutic exposure of contemporary dosing of empirical broad-spectrum β-lactam antibiotics and narrower spectrum antibiotics for a number pathogens for which de-escalation may be considered. The secondary objective was to determine whether alternative dosing strategies improve this probability.

Design: We performed a simulation study using published population pharmacokinetic data in critically ill patients for a number of broad-spectrum β-lactam antibiotics (meropenem and piperacillin) and narrower spectrum antibiotics (amoxicillin, cefuroxime and flucloxacillin). Simulations were undertaken using a dataset obtained from critically ill patients with sepsis without renal failure (n=49). Using the simulated concentration profiles, the time for which the free antibiotic concentration exceeds the minimal inhibitory concentration ($fT_{>MIC}$) was calculated for each subject. The PK/PD target was set at 40% $fT_{>MIC}$ for carbapenems, 50% $fT_{>MIC}$ for penicillins, and 65% $fT_{>MIC}$ for cephalosporins. MIC data were obtained for each antibiotic from EUCAST to determine the probability to achieve a therapeutic exposure, which was described as a fractional target attainment (FTA). This is a clinically relevant descriptor of the likely appropriateness of antibiotic dosing that compares the achievement of the PK/PD target against an MIC distribution. The microorganisms used in this simulation study were microorganisms for which de-escalation is commonly performed.

Results: The FTA for the different antibiotics are shown in figure 1. For the broad spectrum antibiotics, the lowest FTA was 89% for *K. pneumoniae* (piperacillin/tazobactam as an intermittent infusion in a dose of 4g 8 hourly), although this increased to 100% when administered as a prolonged infusion. The FTA for amoxicillin ranged from 79% (*K. pneumoniae*) to 100% depending on the microorganism. The lowest FTA for cefuroxime was 65% for *E. coli*. Flucloxacillin had an FTA of 76% against oxacillin-susceptible *S. aureus*. However, changing the intermittent infusion to a higher dose continuous infusion improved the FTA dramatically. For amoxicillin, this improved FTA from 79% to 100%, for cefuroxime from 65% to 100% and for flucloxacillin from 76% to 100%.

Conclusions: For a selection of microorganisms the probability to achieve therapeutic exposure was overall lower for the narrower spectrum antibiotics using conventional dosing compared to the broad-spectrum antibiotics. However, changing the intermittent infusion to a higher dose continuous infusion improves this probability dramatically.