

**P0303**

**Poster Session I**

**New therapeutic alternatives**

**THE IMPACT OF CREATININE CLEARANCE ON THE DOSING OF POL7080, A NEW MACROCYCLIC ANTIBIOTIC**

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**Objectives**

POL7080 is a new macrocyclic antibiotic specifically aimed at *Pseudomonas aeruginosa*. A population pharmacokinetic model based on phase 1 trial results suggested a dose of 7.5 mg/kg per day for treatment of VAP patients with normal renal function. However, it is unknown whether dose adjustments are necessary in patients with enhanced renal clearance or in patients with impaired renal function. This could be of particular importance in patients with VAP as it is increasingly recognized that some of these patients have an increased clearance and therefore may be inadequately exposed. We determined the influence of changed renal function on exposure and dosing.

**Methods**

Data of 21 subjects with renal impairment (creatinine clearance 18 – 66 ml/min) and rich sampling were analyzed in conjunction with 52 healthy subjects without renal impairment and the relationship between creatinine clearance (CC) and clearance of POL7080 established from the population PK model estimates using regression analysis (GraphPad Prism). An estimate of POL7080 clearance was subsequently determined for several values of CC. Monte Carlo Simulations (MCS) were then performed using different values of the clearance in steady state to determine whether the pharmacodynamic target ( $fAUC/MIC$  of 30) was reached.

**Results**

The relationship between creatinine clearance and clearance of POL7080 could best be described by linear regression, with the equation  $Cl = 1.377 + 0.04197 \times CC$ . Mean values for the 3 volumes of distribution (V) were as follows:  $V_1$  8.82 L,  $V_2$  15.8 L and  $V_3$  8.31 L. Values for clearance increased from 2.64 L/h for a CC of 30 ml/min to 9.77 L/h for a CC of 200 ml/min. MCS indicate a clear effect of CC on the AUC and therefore probability of target attainment. MCS for a dose of 200mg q8h (7.5 mg/kg, 80 kg) at CC 50 ml/min resulted in a  $fAUC/MIC$  of approximately 106 and 62.6 mg.h/L for the average and lower 99% confidence interval, respectively, for a MIC of 1 mg/L. For CC of 180 mL/min these values were 40.1 and 23.3 mg.h/L, respectively.

**Conclusion**

The MCS using a CC of 50 mL/min indicate that dosing adjustment might be necessary for patients with renal impairment. Patients with hyperclearance, such as a subgroup of patients with VAP at the intensive care unit, often have a CC of 150 ml/min or higher. The simulations indicate that at a CC of 180 mL/min a dose of 200mg q8h is still adequate for the majority of patients, but may need an extra dose or higher dose at higher creatinine clearance values.