Meropenem population pharmacokinetics in patients affected by carbapenemase-producing *K. pneumonie*

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Carbapenemase-producing *K. pneumoniae* (KPC) strains are responsible for a high rate mortality in intensive care unit (ICU) patients. The use of a combination therapy, including meropenem, has improved patients' survival, but a high risk of death is still present. The rationale of the present study was to investigate meropenem pharmacokinetics/pharmacodynamics (PK/PD) in ICU patients with KPC infections. Moreover, alternative dosing regimens have been simulated and the corresponding probability of target attainment (PTA) and cumulative response fraciton (CRF) were calculated with regards PK/PD parameters that better describe drug efficacy, namely the time above minimum inhibitory concentration (T>MIC) and the minimum plasma concentration (C_{min}) 4 times above MIC value (C_{min}>4xMIC).

Twenty-seven patients (17 males, mean+/-SD age, 61.8+/-12.6 years) hospitalized at the Infectious Diseases Unit of San Martino Hospital, Genova, were enrolled. The study was approved by the local Ethics Committee and patients signed the informed consent. Meropenem was administered as 3-h i.v. infusions at doses of 1-2 g every 8 or 12 h. Blood samples were obtained before, at the end of meropenem infusion and 1, 3, 5 hours after the end of infusion. Plasma Samples analysis was performed by a HPLC method using a C_{18} 250x4.5mm column. Samples were eluted at 35 °C with a mobile phase consisting of phosphate buffer/acetonitrile (93:7, v/v), at a flow rate of 1 mL/min, and they were monitored with an UV detector set at 298 nm.

Pharmacokinetic analysis of meropenem plasma concentrations was performed according to a non-linear mixed-effects modeling strategy using NONMEM vers. 7.2 software, together with PsN and Xpose4 packages [Di Paolo et al, 2014]. All concentration values were adjusted to their respective 98% values in order to take into account the 2% plasma protein binding of meropenem and PK/PD parameters were calculated (*f*T>MIC and *f*C_{min}>4xMIC). Diagnostic plots and bootstrap analysis were used to judge about model performances. Then, the final model was used to simulate meropenem plasma disposition in 4000 patients according to the procedure previously described [Mouton et al, 2005]. In particular, dosing regimens of meropenem were investigate as a 3-h i.v. infusions (1-2 g every 8 or 12 h), or continuous infusions (1-2 g every 8 h). For all of these regimens, *f*T>MIC and *f*C_{min}>4xMIC values were calculated in 4000 simulated patients, as well as PTA and CRF values.

The final model was able to describe meropenem PK in all of the enrolled patients, as demonstrated by diagnostic plots and bootstrap analysis. Notably, gender and the severity of sepsis were found to have a significant effect on drug clearance (CL), whose typical population values ranged from 6.22 up to 12.04 L/h (mean+/-SD value, 9.38+/-4.47 L/h). Moreover, serum albumin and patients' age affected volume of distribution (Vd), for which the mean+/-SD value accounted for 26.20+/-14.56 L. It is worth noting that mean C*min* value was 7.90+/-7.91 mg/L, suggesting a high interindividual variability and a risk of poor efficacy despite the high drug doses. The following simulation and calculation of CRF values confirmed that only 88% of patients achieved effective C*min*>4xMIC values after short, 3-h i.v. infusions of meropenem 2gx3/day. On the contrary, when the same total daily dose may be administered as a continuous i.v. infusion, 100% of patients may attain the desired C*min*>4xMIC values.

In conclusion, results of the present study demonstrate that several factors may significantly and negatively influence meropenem PK in ICU patients affected by KPC infections. Furthermore, simulations suggest that continuous i.v. infusions have an advantage with respect to short i.v. infusion, because a greater percentage of patients may benefit from effective plasma concentrations.

References: Di Paolo A, et.al. Int J Antimicrob Agents. 2013;42:250-5; Mouton JW, et al. J Antimicrob Chemother. 2005;55:601-7