27th ECCMID Vienna, Austria 22 – 25 April 2017
The congress of ESCMID

Session: P055 PK/PD in preclinical models

Category: 5a. Mechanisms of action, preclinical data & pharmacology of antibacterial agents

24 April 2017, 12:30 - 13:30
P1214

Microdialysis study distribution of aztreonam and avibactam in skeletal muscle and intraperitoneal fluid of rats with and without experimental peritonitis

Alexia Chauzy*[1], Nicolas Gregoire[2], Isabelle Lamarche[2], Patrice Gobin[2], William Couet[2], Sandrine Marchand[2]

[1]*Inserm (Unit U1070); Pharmacology of Antimicrobial Agents*

[2]*University of Poitiers and Inserm*

Background: The purpose of this study was to investigate aztreonam (ATM) and avibactam (AVI) distribution in intraperitoneal fluid and muscle interstitial fluid by microdialysis in rats, with or without peritonitis, and to compare unbound concentrations in tissue with the free concentrations in blood.

Material/methods: Microdialysis probes (CMA 20) were inserted into the jugular vein, hind leg muscle and peritoneal cavity of control rats (n = 5) and rats with intra-abdominal sepsis (n = 9) induced by cecal ligation and punctures. ATM and AVI probe recoveries in each media were determined for both molecules in each rat by retrodialysis by drug. ATM-AVI combination was administered as an intravenous bolus at a dose of 100/25 $mg \cdot kg^{-1}$. Microdialysis samples were collected over 120 min, and ATM-AVI concentrations were determined by LC-MS/MS. Non-compartmental pharmacokinetic analysis was conducted and non-parametric test were used for statistical comparisons between groups (infected versus control) and medium. Experiments were conducted in compliance with EU Directive 2010/63/EU after approval by the local ethic committee (authorization number 2016011111381822).

Results: Intraperitoneal infection had no apparent effect on ATM and AVI pharmacokinetics, and concentration profiles in blood, intraperitoneal fluid and muscle were virtually superimposed, in control rats and in infected animals, for ATM and AVI. No statistically significant differences were observed between total area under unbound concentration-versus-time curves (AUC) shown in Table 1.

Table 1. AUCs ± sd (μg.h.mL^{-1}) in blood, muscle and intraperitoneal fluid of control rats and rats with peritonitis after an IV-bolus of ATM-AVI combination at a dose of 100/25 mg · kg^{-1}

	Aztreonam			Avibactam		
	Blood	Muscle	Intraperitoneal fluid	Blood	Muscle	Intraperitoneal fluid
Control rats (n=5)	131.8 ± 16.8	123.7 ± 7.5	116.2 ± 18.7	39.7 ± 3.5	35.9 ± 4.9	35.1 ± 6.2
Rats with peritonitis (n=9)	152.6 ± 54.0	142.7 ± 46.2	145.6 ± 68.3	41.4 ± 5.7	42.1 ± 8.3	38.8 ± 10.0

Conclusions: ATM and AVI distribution in intraperitoneal fluid and muscle was rapid and complete both in control rats and in rats with peritonitis.