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

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Introduction

- Aztreonam-avibactam (ATM-AVI) is a novel β-lactam-β-lactamase inhibitor combination under development for the treatment of infections, including peritonitis, caused by multidrug-resistant Gram-negative isolates
- Microdialysis studies in peritoneal fluid (PF) have shown that AUCs of imipenem and meropenem in the PF of critical-care patients with peritonitis, were lower than their corresponding plasma AUCs, due to peripheral degradation [1,2]. Therefore unbound PF concentrations should be better predictors of antibiotic efficacy than unbound plasma levels.
- The aim of this study was to investigate ATM and AVI distribution within PF and muscle interstitial fluid by microdialysis, in rats with or without peritonitis, and to compare peripheral unbound concentrations with unbound concentrations in blood.

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 peritonitis (n=9) induced by cecal ligation and punctures [3].
- *In vivo* recoveries of ATM and AVI were determined in each media and each rat by retrodialysis by drug.
- ATM-AVI combination was administered as an IV bolus in a 4:1 ratio at a dose of 100-25 mg · kg^{-1}.
- Microdialysis samples were collected every 10 min over 120 min, and ATM-AVI concentrations were assayed by LC-MS/MS.
- Non-compartmental pharmacokinetic analysis was conducted and non-parametric tests were used for statistical comparisons between groups (infected versus control) and between medium (blood, PF and muscle).

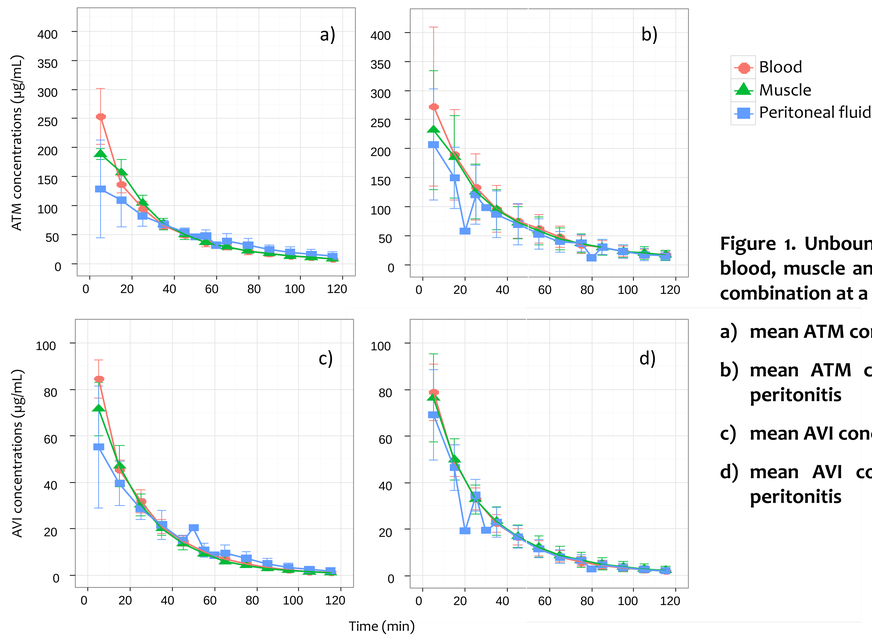

Figure 1. Unbound ATM and AVI concentrations in blood, muscle and PF after an IV-bolus of ATM-AVI combination at a dose of 100-25 mg · kg^{-1}:

a) **mean ATM concentrations ± SD in control rats**
b) **mean ATM concentrations ± SD in rats with peritonitis**
c) **mean AVI concentrations ± SD in control rats**
d) **mean AVI concentrations ± SD in rats with peritonitis**

Results

- ATM probe recoveries were equal to 30.1% ± 11.1% in blood, 27.7% ± 9.4% in muscle and 30.5% ± 10.4% in PF.
- AVI probe recoveries were equal to 45.7% ± 11.1% in blood, 39.5% ± 8.0% in muscle and 41.2% ± 10.6% in PF.
- Intraperitoneal infection had no apparent effect on ATM and AVI pharmacokinetics.
- Unbound concentrations versus time profiles in blood, muscle and PF were virtually superimposed, both in control rats and infected animals, and for ATM as well as AVI (Figure 1).
- AUCs of ATM and AVI were not statistically different between blood, muscle and PF, and AUC ratios were close to 1 for both groups (Table 1).

Table 1. ATM and AVI unbound PK parameters values estimated in blood, muscle and PF 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						
Parameter	Control rats			Rats with peritonitis		
	Blood	Muscle	Intraperitoneal fluid	Blood	Muscle	Intraperitoneal fluid
C_{max} (µg·mL^{-1})	254 ± 48	192 ± 7	136 ± 78	274 ± 136	235 ± 99	210 ± 93
$t_{1/2}$ (min)	25.8 ± 4.7	26.4 ± 7.1	33.2 ± 10.3	30.2 ± 2.9	30.8 ± 5.6	31.0 ± 4.1
AUC (µg·h·mL^{-1})	132 ± 17	124 ± 8	116 ± 19	181 ± 75	170 ± 64	151 ± 66
AUC_{tissue}/AUC_{blood}		0.95 ± 0.12	0.89 ± 0.14		1.00 ± 0.30	0.92 ± 0.41

AVIBACTAM						
Parameter	Control rats			Rats with peritonitis		
	Blood	Muscle	Intraperitoneal fluid	Blood	Muscle	Intraperitoneal fluid
C_{max} (µg·mL^{-1})	84.5 ± 8.2	71.6 ± 11.5	55.1 ± 26.3	78.7 ± 12.2	76.8 ± 17.9	69.1 ± 19.4
$t_{1/2}$ (min)	18.8 ± 2.9	18.1 ± 2.9	21.4 ± 5.0	21.4 ± 3.0	22.4 ± 4.7	22.8 ± 4.4
AUC (µg·h·mL^{-1})	39.7 ± 3.5	35.9 ± 4.9	35.1 ± 6.2	41.4 ± 5.7	42.1 ± 8.3	38.8 ± 10.0
AUC_{tissue}/AUC_{blood}		0.91 ± 0.11	0.88 ± 0.11		1.01 ± 0.14	0.94 ± 0.21

Conclusions

- ATM and AVI distribution in PF and muscle was rapid and there was no significant difference between unbound peripheral and systemic AUCs, suggesting the lack of peripheral degradation, in particular within PF both in the absence and presence of infection induced by cecal ligation and puncture.
- Consequently in this experimental infection model, unbound blood concentrations reflect unbound concentrations at the infection site.

References

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