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Maxime Vallée, Céline Barc, Jérémy Moreau, Nathalie Kasal-Hoc, Isabelle Lamarche, et al.. Tissue distribution of Ceftazidime-Avibactam in kidney tissue in healthy rats and pigs using a microdialysis technique. 34th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Apr 2024, Barcelona, Spain. hal-04571042

HAL Id: hal-04571042

<https://hal.science/hal-04571042>

Submitted on 7 May 2024

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Tissue distribution of Ceftazidime-Avibactam in kidney tissue in healthy rats and pigs using a microdialysis technique

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Introduction

- For about a decade, health authorities around the world are concerned by antibiotic resistance. Experts from the WHO predict that in 2050 the incidence of morbidity due to infectious diseases will be similar to that of the 1940's if nothing is done [1]. Uropathogenic bacteria are particularly involved in these antibiotic resistance phenomena.
- Ceftazidime-avibactam (CAZ-AVI) is a novel β -lactam- β -lactamase inhibitor combination designed for the treatment of urinary tract and digestive infections caused by multidrug-resistant Gram-negative isolates [2].
- The aim of this study was to predict human CAZ/AVI tissue concentrations based on data obtained in rats and pigs using a physiologically based (PBPK) modelling approach. This abstract presents the initial step corresponding to the study of the *in vivo* kidney distribution of CAZ/AVI in healthy rats and pigs following a single i.v. dose.

Methods

- Experiments were approved by the local ethics committees and registered by the French Ministry of Higher Education and Research.
- Under general anesthesia, microdialysis probes (CMA 20 (membrane length 1 cm in blood and muscle and 3mm in kidney) and CMA 63 (membrane length 1 cm) microdialysis catheters, respectively for rats and for pigs), were inserted into blood, muscle and kidney (pictures 1 and 2) using open surgery (for rats and pigs) or interventional sonography (only for pigs ; picture 3) (n=5 rats (Sprague Dawley) and 5 pigs (Large White)).
- The perfusion flow rate was 0.5 μ L/min for all the duration of experiment. The pharmacokinetic experiment started with a retrodialysis by drug period during which all probes were perfused with ringer containing CAZ/AVI to determine the *in vivo* recovery by loss of probes [3] for each animal.
- Single dose of CAZ/AVI (respectively, 20 mg/kg of CAZ and 5 mg/kg of AVI as an i.v bolus in rats and 40 mg/kg of CAZ and 10 mg/kg of AVI as a 2 hours infusion in pigs) was administered. Then, microdialysis samples were taken every 10 minutes for 1 hour, then every 30 minutes for the remaining 2 hours in rats, and every half-hour for 6 hours in pigs. CAZ/AVI assays in the dialysates was performed by LC-MS/MS.
- Pharmacokinetic parameters were determined in each individual rat by a noncompartmental approach according to standard procedures (package R PKNCA) where area under the curve in all media (AUC_{muscle}, AUC_{blood}, AUC_{kidney}) were calculated using trapezoidal rule.

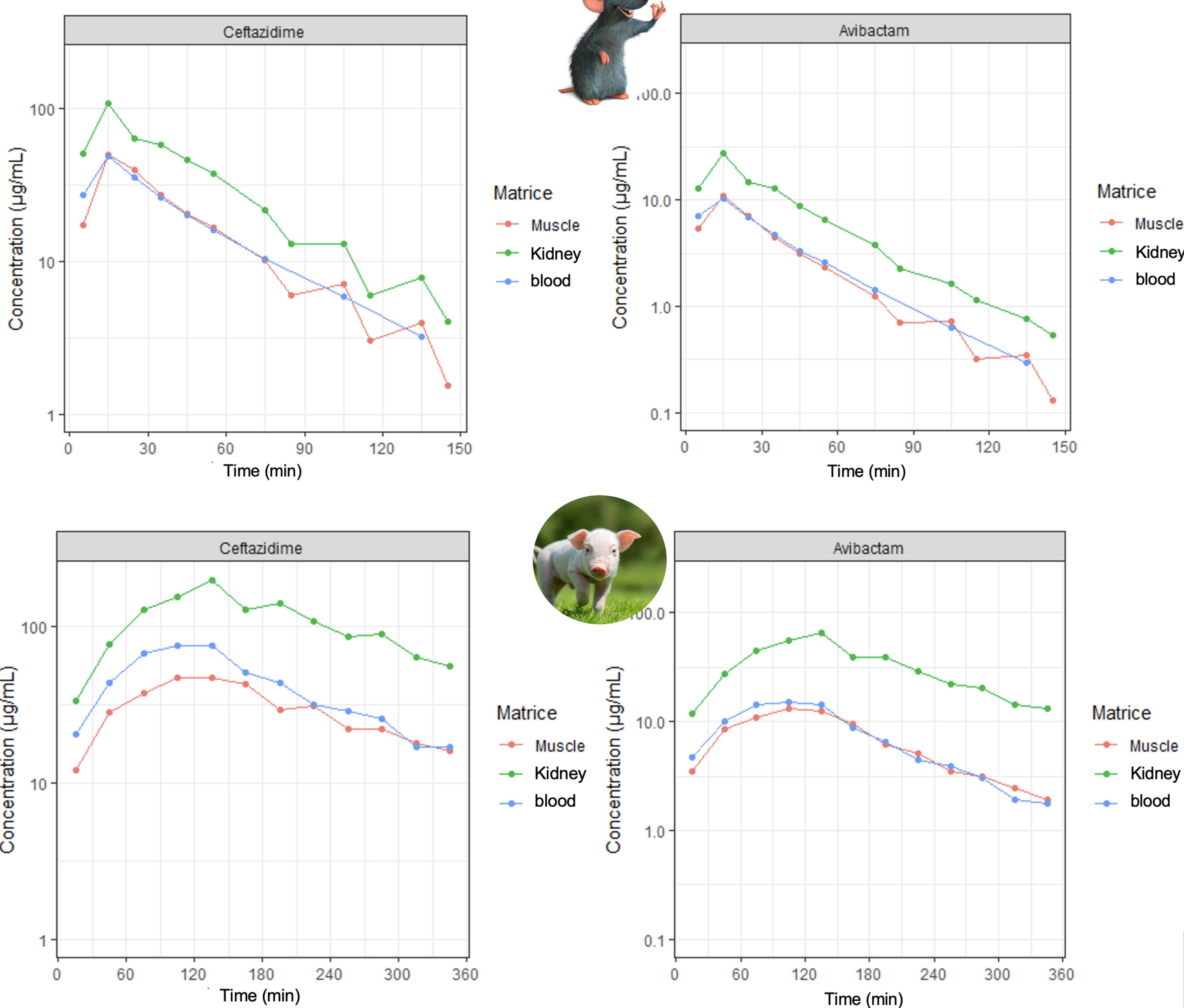
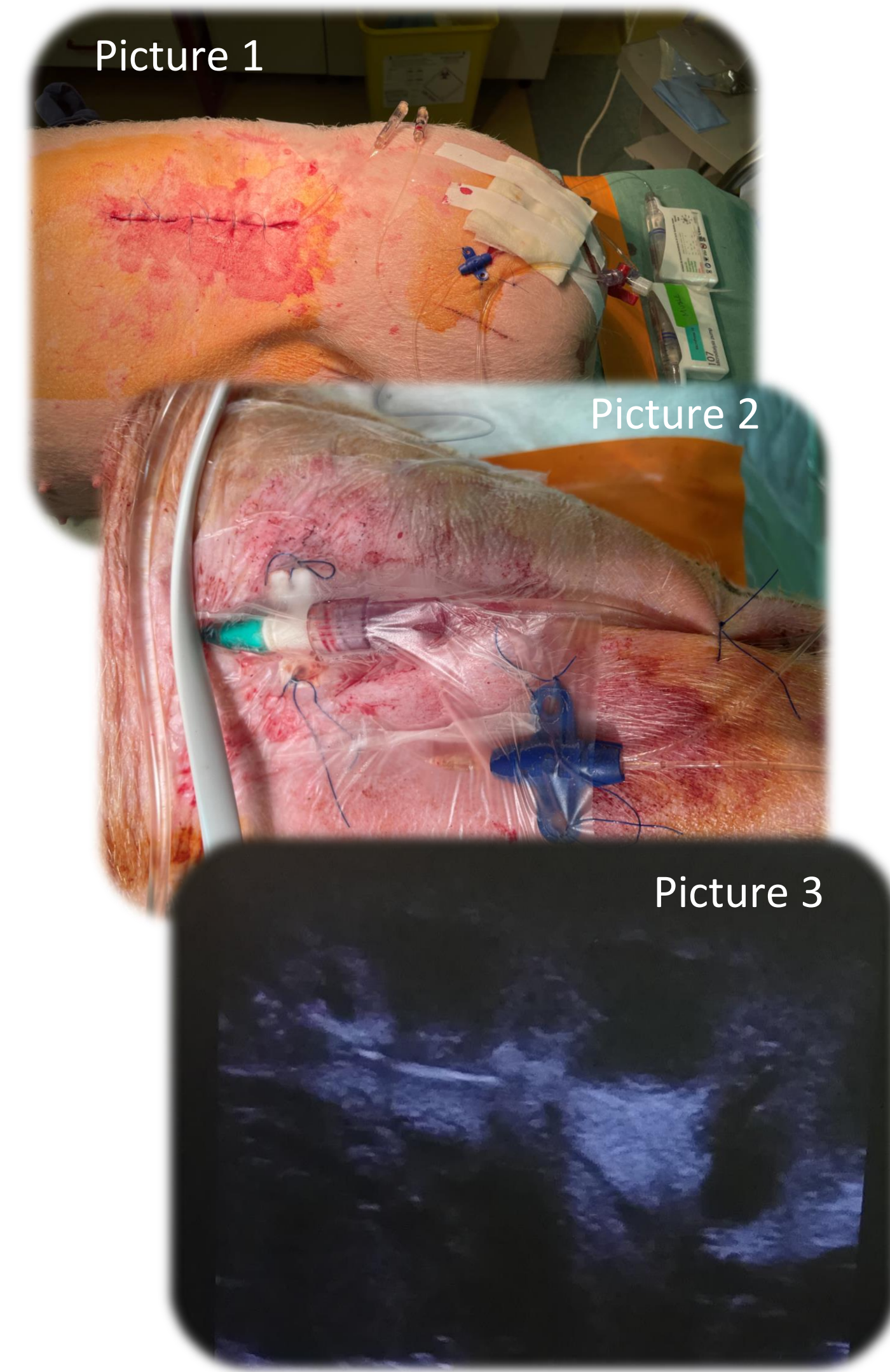


Figure 1. Mean unbound CAZ and AVI concentrations in blood, muscle and kidney after an IV-single dose of CAZ-AVI.

Results

- In both species, CAZ and AVI *in vivo* recovery by loss (RL_{in vivo}) differed between animals for a same medium and between different media for a same animal.
- Probe recoveries were generally lower for CAZ than for AVI in both species too, possibly because AVI has a lower molecular weight than CAZ.
- In both rats and pigs, the decay of CAZ and AVI concentrations as a function of time was monoexponential and the concentrations profiles were almost superimposed in muscle and blood (Figure 1).
- CAZ and AVI ratios of muscle on blood (AUC_{muscle}/AUC_{blood}) were close to one, suggesting a similar drug exposure. In rats, there was no delay in diffusion of the CAZ/AVI into the kidneys but kidney concentrations of CAZ and AVI were higher than those in blood, characterized by AUC ratios (AUC_{kidney}/AUC_{blood}) higher than one, respectively equal to 2.1 and 2.4. Same observations were performed in pigs with AUC_{kidney}/AUC_{blood} = 2.5 and 4.3 respectively for CAZ and AVI (Figure 1).

Conclusion

- CAZ/AVI distribute rapidly in muscle and kidneys in both species.
- Kidney exposure to CAZ is twice as high as blood in rats and pigs while AVI exposure is 2 to 4 times higher in rats and pigs respectively.
- A study on a cellular model is currently underway to try and explain these observations.
- These results will be used to predict renal concentrations of CAZ/AVI in patients using a physiological modeling approach (PBPK).

[1] World Health Organization, Antimicrobial resistance: global report on surveillance. 2014

[2] Chapelle C, et al. Antibiotics. 2021 Nov 1;10(11):1332.

[3] Chauzy A et al. Antimicrob Agents Chemother. 2018 Sep 24;62(10):e01228-18.

