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Population pharmacokinetics of ceftazidime-avibactam among critically-ill patients with and without receipt of continuous renal replacement therapy

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INTRODUCTION

- Ceftazidime-avibactam (CAZ-AVI) is a β-lactam/β-lactamase inhibitor combination used to treat multidrug-resistant Gram-negative infections
- Pharmacokinetic data are limited among critically ill patients treated with CAZ-AVI
- There are no standard dosing recommendations for patients receiving continuous renal replacement therapy (CRRT)
- We have previously shown that suboptimal dosing during CRRT may be associated with the emergence of CAZ-AVI resistance
- Our objective was to investigate CAZ and AVI exposures among critically-ill patients at our center, including those receiving CRRT during treatment

METHODS

- **Enrollment:** Twenty patients at our center were enrolled between 2016 and 2019
  - All patients received ≥48h of CAZ-AVI before sampling
    - Doses were determined by the treating provider
  - CRRT settings are shown in Table 5 at the time of sampling
  - Patients were monitored for toxicity during therapy
- **Sampling:** Serial blood samples were collected pre-dose and at 2, 4, 6, and 8 hours after CAZ-AVI administration. All doses were administered over a standard 2-hour infusion.
- **Quantification:** Samples (n=96) were analyzed simultaneously by LCMS for CAZ and AVI using a validated assay. The assay was linear over a range of 0.1 – 20µg/mL of AVI and 1 – 200µg/mL CAZ.
- **Analysis:** Minimum (C_{min}) and maximum concentrations (C_{max}), area under the curve (AUC), elimination rate (K_e), half life ($t_{1/2}$), volume of distribution (V_d), and clearance (CL) were calculated for each patient. Free drug concentrations were estimated assuming 10% protein binding for both CAZ and AVI. GraphPad 8.0 was used for statistical analysis and Phoenix WinNonlin version 8.2 for pharmacokinetic analyses.

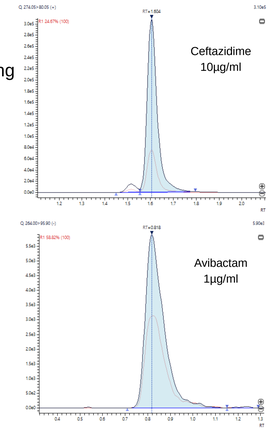


Figure 1: Chromatograms of CAZ and AVI.

RESULTS

Table 1. Patient Demographics (n=20)

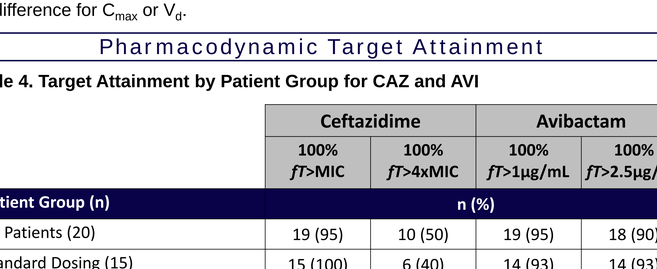
	Patient	Age	Sex	Race[1]	Height (cm)	Weight[2] (kg)	Dose	SCr[3]	Cockroft-Gault CrCl (ml/min)	RRT
Non Standard	7	74	F	D	160	50.9	0.94g q 24h	2.3	CRRT	CRRT
	2	64	M	W	178	66	0.94g q 48h	2	HD	HD
	5	69	F	W	173	54.5	0.94g q 48h	2.1	HD	HD
	1	60	M	W	185	120.8	1.25g q 8h	2.1	42.0	None
	16	51	F	W	168	65.7	1.25g q 8h	1.5	42.0	None
	Mean	63.6			172.8	71.6		1.93		
Standard	3	59	F	W	163	70.1	2.5g q 8h	1	52.6	None
	4	59	F	W	163	78.2	2.5g q 8h	0.6	87.7	None
	6	59	F	W	185	85.8	2.5g q 8h	0.7	133.5	None
	8	66	M	W	175	132	2.5g q 8h	0.4	CRRT	CRRT
	9	68	M	W	175	75.6	2.5g q 8h	1.2	CRRT	CRRT
	10	48	F	W	173	67	2.5g q 8h	1.5	CRRT	CRRT
	11	35	M	W	163	66	2.5g q 8h	1	CRRT	CRRT
	12	59	M	U	170	120	2.5g q 8h	1.5	CRRT	CRRT
	13	58	M	W	178	96	2.5g q 8h	1.5	CRRT	CRRT
	14	45	F	W	163	46.2	2.5g q 8h	0.4	154.2	None
	15	44	F	W	168	132	2.5g q 8h	0.4	168.6	None
	17	31	M	W	193	75.5	2.5g q 8h	0.7	187.1	None
	18	61	M	W	168	104.6	2.5g q 8h	1	70.2	None
	19	41	M	W	171	73.2	2.5g q 8h	2.5	36.8	None
	20	63	M	W	177	114	2.5g q 8h	0.8	96.3	None
	Mean	53.1			172.3	89.0		1.01		
	Overall Mean	55.7			172.4	84.7		1.21		

patients when >120% IBW ; [3]Serum creatinine (SCr) on day of sampling ; Hemodialysis

RESULTS

Ceftazidime Pharmacokinetics

Figure 2: CAZ concentration-time profiles for individual patients receiving standard doses of 2.5g IV q 8h with (right panel) or without (left panel) CRRT



- C_{min} was higher for patients on a standard dose receiving CRRT compared to those with normal renal function (46.59 vs 29.01, p = 0.0496). A longer half life was also observed (10.12h vs 4.478h, p = 0.0496) and K_e was lower for those on CRRT (0.07 vs 0.15, p = 0.0496). There was no statistical difference for C_{max}, AUC, CL and V_d.

Table 2. Calculated Ceftazidime PK Parameters by Patient Group.

Median (IQR)	All patients (n=20)	Standard Dose			Other (n=5)
		All 2.5g q8h (n=15)	CrCl > 50ml/min (n=9); 2.5g IV q8h	CRRT (n=6); 2.5g IV q8h	P value
C_{max} (µg/ml)	80.6 (61.2, 104.1)	87.0 (69.2, 108.2)	81.3 (76.5, 88.1)	96.3 (69.6, 112.4)	0.4559	69.9 (59.3, 73.2)
C_{min} (µg/ml)	40.4 (28.3, 55.0)	35.4 (27.7, 53.5)	29.0 (20.9, 35.5)	46.6 (37.9, 64.4)	0.0496	46.1 (46.0, 53.7)
$AUC_{0\text{-}8h}$ (hr*µg/mL)[1]	456.3 (400.3 588.1)	456.6 (388.7, 651.8)	437.4 (328.2, 550.3)	522.2 (455.1, 683.7)	0.3277	444.8 (432.7, 456.9)
K_e (1/hr)	0.13 (0.06, 0.16)	0.15 (0.10, 0.16)	0.15 (0.14, 0.19)	0.07 (0.05, 0.14)	0.0496	0.04 (0.04, 0.07)
$t_{1/2}$ (hr)	5.2 (4.3, 12.6)	4.5 (4.2, 7.0)	4.5 (3.7, 5.1)	10.1 (5.5, 15.1)	0.0496	15.7 (8.9, 16.5)
V_d (L)	34.6 (22.5, 49.3)	28.7 (20.6, 46.0)	26.0 (16.3, 36.1)	43.2 (31.3, 56.9)	0.1135	40.7 (33.1, 55.1)
CL (L)	3.6 (2.3, 5.2)	4.4 (3.2, 5.5)	5.3 (3.6, 6.2)	4.0 (3.0, 4.7)	0.2238	2.3 (1.8, 2.3)

[1]Patients with 24 or 48 hour dosing (n=3) were excluded. Total patients = 17, Other = 2. 1

Avibactam Pharmacokinetics

Figure 3: Avibactam concentration-time profiles for individual patients receiving standard dose with (right panel) or without (left panel) CRRT

- For patients on a standard dose with normal renal function compared to those on CRRT, C_{min}, AUC, $t_{1/2}$, K_e, and CL were statistically different (normal function vs CRRT, respectively: 4.45 vs 11.1, p = 0.0028, 73.4 vs 126.4, p = 0.0496, 3.3 vs 10.3, p = 0.0048, 0.21 vs 0.07, p = 0.0048, 6.6 vs 4.2, p = 0.0256). There was no statistical difference for C_{max} or V_d.

Table 3. Calculated Avibactam PK Parameters by Patient Group.

Median (IQR)	All patients (n=20)	Standard Dose			Other (n=5)
		All 2.5g q8h (n=15)	CrCl > 50ml/min (n=9); 2.5g IV q8h	CRRT (n=6); 2.5g IV q8h	P value
C_{max} (µg/ml)	15.6 (11.8, 23.0)	15.9 (12.7, 24.3)	13.3 (11.3, 16.3)	21.3 (16.7, 27.1)	0.1135	14.1 (8.9, 21.5)
C_{min} (µg/ml)	8.5 (4.2, 9.8)	8.9 (3.9, 10.1)	4.5 (2.8, 8.9)	11.1 (9.8, 14.2)	0.0028	6.11 (5.8, 9.0)
$AUC_{0\text{-}8h}$ (hr*µg/mL)[1]	98.8 (58.3, 149.4)	99.1 (62.0, 150.2)	73.4 (48.3, 99.1)	126.4 (101.9, 154.5)	0.0496	74.7 (66.5, 82.9)
K_e (1/hr)	0.15 (0.07, 0.21)	0.16 (0.09, 0.21)	0.21 (0.16, 0.23)	0.07 (0.05, 0.13)	0.1135	0.07 (0.05, 0.07)
$t_{1/2}$ (hr)	4.6 (3.3, 10.2)	4.4 (3.3, 7.9)	3.3 (3.0, 4.2)	10.3 (5.6, 15.2)	0.0048	9.8 (9.3, 12.6)
V_d (L)	43.2 (23.4, 58.9)	38.1 (22.6, 56.8)	32.1 (20.6, 43.8)	56.1 (35.4, 78.9)	0.1135	43.8 (42.6, 57.7)
CL (L)	4.5 (3.3, 6.2)	5.3 (3.4, 8.0)	6.6 (5.6, 9.6)	4.2 (3.3, 4.9)	0.0256	3.0 (1.6, 3.6)

[1]Patients with 24 or 48 hour dosing (n=3) were excluded. Total patients = 17, Other = 2.

Pharmacodynamic Target Attainment

Table 4. Target Attainment by Patient Group for CAZ and AVI

	Ceftazidime		Avibactam	
	100% *f*T>MIC	100% *f*T>4xMIC	100% *f*T>1µg/mL	100% *f*T>2.5µg/mL
Patient Group (n)	n (%)			
All Patients (20)	19 (95)	10 (50)	19 (95)	18 (90)
Standard Dosing (15)	15 (100)	6 (40)	14 (93)	14 (93)
Standard, Normal Renal Function (9)	9 (100)	2 (22)	8 (89)	8 (89)
Standard, CRRT (6)	6 (100)	4 (67)	6 (100)	6 (100)
Non Standard Dosing (5)	4 (80)	4 (80)	5(100)	5(100)

- CLSI susceptibility breakpoint of 8µg/mL was used as the MIC for *f*T>MIC for CAZ
- Surrogate targets were used for AVI as pharmacodynamics targets are not well-established for β-lactamase inhibitors

Renal Replacement Therapy

Table 5. Details and Outcomes for Patients on CRRT

Patient	Blood Flow Rate (mL/hr)	Replacement Fluid Infusion Rate (mL/hr)	Dialysate Flow Rate (mL/hr)	Dialysate Flow Rate (mL/kg/hr)	Duration of CAZ-AVI during CRRT	Clinical Outcome
7[2]	250	250	1750	34.4	2 days	Died on day 7 of treatment (w/in 48h of sampling)
8	250	250	3000	22.7	2 days	Died on day 5 of treatment (w/in 72h of sampling)
9	200	500	3000	39.7	14 days	Completed treatment, no AEs[3]
10	250	250	1500	22.4	3 days	De-escalated to meropenem, no AEs
11	250	250	1700	25.8	4 days	Died on day 5 of treatment (w/in 48h of sampling)
12	300	250	3500	29.2	14 days	Completed treatment, no AEs
13	250	250	2500	26.0	10 days	Completed treatment, no AEs

[1]Prismaflex with M100 filter for all patients except patient 12 (filter model M150) ; [2]Non standard dose, 0.94g q24h ; [3]Adverse events (AEs)

CONCLUSIONS

- Therapeutic concentrations of CAZ-AVI were achieved in critically-ill patients
- Among patients receiving CRRT, doses of 2.5g IV q 8h were tolerated within the durations of therapy used and resulted in longer steady-state half-lives, higher trough concentrations, and achievement of optimal pharmacodynamics targets
- Given the potential risks of treatment failure and emergence of resistance, we recommend a dose of 2.5g IV q 8h for patients on CRRT with close monitoring for toxicity to achieve optimal pharmacodynamics targets

ACKNOWLEDGEMENTS

Study was supported by an investigator-initiated grant from Allergan Pharmaceuticals