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Continuous infusion and outpatient parenteral antimicrobial therapy with ceftazidime-avibactam: evaluation of efficacy based on therapeutic drug monitoring

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Background: Based on recent PK/PD evidence, continuous infusion (CI) of beta-lactam administration is increasingly recommended for serious infections. Since 2016, the combination of ceftazidime and avibactam (CAZ/AVI) is administered per manufacturer prescription as an intermittent infusion of 2,5g every 8 hours thus CI has not yet been evaluated in clinical trials.

Materials/methods: We aimed to evaluate the use of CI of CAZ/AVI in a retrospective case series, from December 2016 to October 2019. All isolates displayed *in vitro* susceptibility to CAZ/AVI in agreement with EUCAST breakpoint. Patients were initially given CAZ/AVI as CI of 5g q12h. CAZ/AVI dosages were adjusted according to therapeutic drug monitoring (TDM) of ceftazidime with a therapeutic goal of 4-5xT> MIC in the plasma and/or at the site of infection. The latter was extrapolated from plasma concentrations and literature data

Results: CAZ/AVI was administered as CI in ten of thirty-three infectious episodes in twenty-seven patients treated with CAZ/AVI in our hospital. These infections were mainly caused by *Pseudomonas aeruginosa* (54,5%). Bacteremia occurred in 30% of cases and septic shock was only present in one patient. CAZ/AVI was used as monotherapy in 60% of cases. Clinical cure or improvement was achieved in 70 % of cases and microbiological cure was achieved in 6/7 (86%) evaluable cases (Table 1). Thirty days after the CAZ/AVI treatment onset, two patients (20%) had died, with death possibly related to uncontrolled infection in one case. Three patients were discharged home with an outpatient parenteral antimicrobial therapy (OPAT). Based on repeated TDM (3,5 samples/patient), therapeutic goals were achieved in 100% of cases in plasma and 88% of cases at the site of infection (8/10 evaluable), CAZ/AVI looked stable for 12-hour infusions and no drug-related adverse events were noted.

Conclusions: Although the sample size was limited, our case series shows promising clinical results for CI of CAZ/AVI, including for OPAT. Based on repeated TDM, therapeutic goals were achieved in 100% of cases in plasma. CAZ/AVI looked stable for 12-hour infusions and no drug-related adverse events were noted.

Table 1 - Ceftazidime-avibactam administered as continuous infusion

Patient	Type of infection	Type of organisms	CAZ/AVI MIC (mg/L)	Daily dose of CAZ/AVI (g)	Therapeutic goals 4-5xT > MIC (mg/L)		TDM of ceftazidime, mean (mg/L)	Sample of ceftazidime TDM /patient (n)	Duration of CAZ/AVI as CI (days)	OPAT	Clinical response	Microbiological response
					Plasma	Site of infection						
1	Bone and joint infection	KPC-producing *Klebsiella pneumoniae*	2	10	8 - 10	24 - 30	35,1	5	25	Yes	Cured	Cured
2	cUTI and bacteremia	KPC-producing *Klebsiella pneumoniae*	8	7,5 for 18 days 5 for 5 days	32 - 40	32 - 40	47,6 (7,5g daily) 44,6 (5g daily)	4	23	Yes	Cured	NE
3	VAP	*Pseudomonas aeruginosa*	8	10	32 - 40	96 - 120	84,3	5	24	No	Improved	Cured
4	VAT	*Pseudomonas aeruginosa*	8	5	32 - 40	NA	82,0	2	5	No	Cured	NE
5	VAT	*Pseudomonas aeruginosa*	0,5	10	2 - 2,5	NA	124,0	1	3	No	Improved	Cured
6	cIAI	*Enterobacter aerogenes*	6	5	24 - 30	48 - 60	>80	2	7	No	Relapse	Cured
7	VAP	ESBL-producing *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*	1 (ESBL-producing *Klebsiella pneumoniae*) 2 (*Pseudomonas aeruginosa*)	10	8 - 10	24 - 30	76,2	2	7	No	Cured	Cured
8	cUTI	ESBL-producing *Klebsiella pneumoniae*	0,25	5	1 - 1,25	7 - 8,75	17,6	7	37	Yes	Cured	NE
9	prothesis joint infection and bacteremia	*Pseudomonas aeruginosa*	4	7,5	16 - 20	48 - 60	56,7	4	12	No	Failure	Failure
10	cIAI and bacteremia	*Pseudomonas aeruginosa*	2	10	8 - 10	16 - 20	67,4	3	12	No	Relapse	Cured

Abbreviations: CAZ/AVI, ceftazidime-avibactam; MIC, minimum inhibitory concentration ; TDM, therapeutic drug monitoring ; CI, continuous infusion; OPAT, outpatient parenteral antimicrobial therapy; cUTI, complicated urinary tract infection; cIAI, complicated intra-abdominal infection; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis; ESBL, extended-spectrum beta-lactamases; NA, not applicable; NE, not evaluable.

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