Establishing Pharmacokinetic Profile of β-lactams in Critically Ill Patients on Continuous Sustained Low-efficiency Dialysis (C-SLED)

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BACKGROUND

- Critically-ill patients often require renal replacement therapy (RRT) due to volume overload, metabolic acidosis, acute kidney injury (AKI) due to multi-organ failure, or electrolyte abnormalities.
- There are various modalities of RRT, and the most common ones used in the intensive care unit are intermittent hemodialysis (iHD), continuous renal replacement therapy (CRRT), or sustained low-efficiency dialysis (SLED)
- Continuous SLED (C-SLED) is a new modality that allows patient mobility, has less risk of bleeding, and requires conventional equipment compared to CRRT.
- There is lack of pharmacokinetic and pharmacodynamics data in C-SLED which causes the uncertainty of efficacy with the current dosing strategies.

OBJECTIVES

Evaluate patient-specific pharmacokinetic parameters of various β-lactam antibiotics in critically ill patients on C-SLED to assess if the current dosing strategy leads to therapeutic drug levels.

METHODS

Prospective, observational, single center pharmacokinetic study
Inclusion criteria
- Age >18 years
- In the intensive care unit for >24 hours
- On Sustained Low Efficiency Dialysis in the Continuous Mode (C-SLED)
- Receiving β-lactam antibiotics
- Has at least one drug level

Exclusion criteria
- Pregnant Women
- Prisoners

Statistical analysis
- Descriptive statistics

OUTCOMES

- Number of patients with drug levels within the therapeutic range.
- Patient specific co-efficient of elimination, half-life, and clearance.

THERAPEUTIC DRUG TARGETS

Effect	Penicillin (%)	Cephalosporin (%)	Carbapenem (%)
Bacteriostatic (%fT>MIC)	30	35-50	20
Bactericidal (%fT>MIC)	50	60-70	40
Critically ill patients (%fT>MIC)	100	100	100

RESULTS

TABLE 1: BASELINE CHARACTERISTICS

Characteristics	All patients (n = 11)
Male sex, n (%)	9 (81.8)
Age, years, Median (IQR)	55 (19.7)
Antibiotic Use, n (%)	
Empiric	10 (71.4)
Targeted	4 (28.6)
Escherichia coli	1 (25)
Pseudomonas aeruginosa	2 (50)
Klebsiella oxytoca	1 (25)
Staphylococcus aureus	1 (25)
Hospital Length of Stay, Days, Median (IQR)	50 (32.5)
Dialysate flow rate, mL/min, Median (IQR)	200 (0)
Blood flow rate, mL/min, Median (IQR)	300 (50)
Dosing, n (%)	
CrCL >50mL/min	10 (77)
CrCL 30-50mL/min	3 (23)

RESULTS

TABLE 2: THERAPEUTIC DRUG MONITORING OUTCOMES

Variables	All Patients n (%)	CrCL >50mL/min n (%)	CrCL 30-50mL/min n (%)
Achieved Therapeutic Target (%fT>MIC)	13 (100)	10 (100)	3 (100)
Penicillins (50% fT>MIC)	3 (100)	3 (100)	0
Cephalosporins (60% fT>MIC)	6 (100)	4 (100)	2 (100)
Carbapenems (40% fT>MIC)	4 (100)	3 (100)	1 (100)

TABLE 3: THERAPEUTIC DRUG MONITORING OUTCOMES (Target = 100% fT >MIC)

Variables	All Patients n (%)	CrCL >50mL/min n (%)	CrCL 30-50mL/min n (%)
Achieved Therapeutic Target	8 (61.5)	7 (70)	1 (33)
Penicillins	1(33)	1 (33)	0
Cephalosporins	4 (66.7)	3 (75)	1 (50)
Carbapenems	3 (75)	2 (67)	1 (100)

TABLE 4; β-LACTAMS ANTIMICROBIALS USED WITH PHARMACOKINETIC AND PHARMACODYNAMICS PARAMETERS

Subject No.	Dose	Cmax (mg/L)	Cmin (mg/L)	Elimination constant (hr-1)	Half-life (hrs)	Clearance (L/hr)	Therapeutic Target (%fT >MIC)
Piperacillin/tazaobactam							
1	3.375g q8h*	154	27	0.43	1.6	11.5	65%
2	3.375g q8h	170	16	0.33	2.0	8.1	87%
3	3.375g q8h*	99	49	0.17	3.9	3.2	100%
Cephalosporins							
4	Cefazolin 2g q8h	255	123	0.10	6.8	6.6	100%
5	Cefazolin 2g q8h	255	146	0.10	6.6	6.8	100%
6	Cefepime 2g q8h	40.1	7.64	0.22	3.1	4.9	91%
7	Cefepime 2g q12h	47.5	11.7	0.18	3.7	5.4	79%
8	Ceftazidime/ avibactam 1.25 q8h	88.8	21	0.22	3.1	3.8	100%
9	Ceftolozane/ tazobatam* 3g q8h	48.1	25	0.14	4.7	1.9	100%
Meropenem							
10	1g q12h	30	5	0.14	4.8	2.9	100%
11	1g q8h	47	6	0.29	2.3	5.9	100%
12	1g q8h*#	81	<5	0.46	1.5	9.3	?**
13	1g q8h*	29	13	0.16	4.2	3.3	100%

*** Extended Infusion, # disruption in C-SLED, **unclear %fT>MIC since trough was <5**

CONCLUSION

- β-lactam daily dose based on CrCL of >30mL/min leads to bactericidal therapeutic drug levels for patients on C-SLED.
- Higher therapeutic drug target (100%fT>MIC) was not achieved in all cases with either dosing strategy.
- Further studies are needed to draw definite conclusion

FUTURE DIRECTION

- Increase sample size
- Analyze clearance by checking drug levels in dialysate fluid
- Monte Carlo simulation to estimate probability of target attainment
- Include other antimicrobials
- Monitor clinical outcomes

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