ID # 628

Utilizing Cefepime Therapeutic Drug Monitoring for Patients at Risk of or Exhibiting Signs of Neurotoxicity

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Background

- Cefepime-induced neurotoxicity (CIN) is theorized to be due to competitive inhibition of γ-amino butyric acid receptors in the CNS.[1]
- Symptoms are often associated with decreased clearance in the setting of renal impairment and increased CNS penetration due to dysfunction of the blood-brain barrier.[2]
- Risk factors include renal impairment, pre-existing CNS disease, co-administration with other neurotoxic medications, and high doses for a prolonged duration. [3-5]
- Therapeutic drug monitoring has been suggested to adjust for inter- and/or intra-individual pharmacokinetic variability, to help minimize the incidence or duration of neurotoxicity.[6]
- A position paper released by an international panel representing ESICM, ESCMID, IATDMCT, and ISAC in 2020 recommends routine TDM for beta-lactams in critically ill patients with a threshold for toxicity of > 20 mg/dL.[6]

Objective

To analyze the association between high trough levels and risk factors for CIN, and the utility of therapeutic drug monitoring in guiding cefepime therapy

Outcomes

Primary Outcome: Incidence of trough levels ≥ 20 mg/dL in patients with possible signs of or with risk factors for CIN

Secondary Outcome: Proportion of patients whose therapy are altered in response to therapeutic drug monitoring

Methods

Study Design	• Single center • Observational chart review

Inclusion Criteria	• Age ≥ 18 years
	• Exhibiting signs of possible CIN
	• At least one of the following:
	  ○ Cefepime ≥ 4 grams/day for ≥ 4 days
	  ○ Renal impairment
	  ○ Pre-existing CNS disease
	  ○ Co-administration with neurotoxic medications
	• Confirm therapeutic dosing

Exclusion Criteria	• Hospice or end-of-life care • Pregnancy

Baseline Characteristics

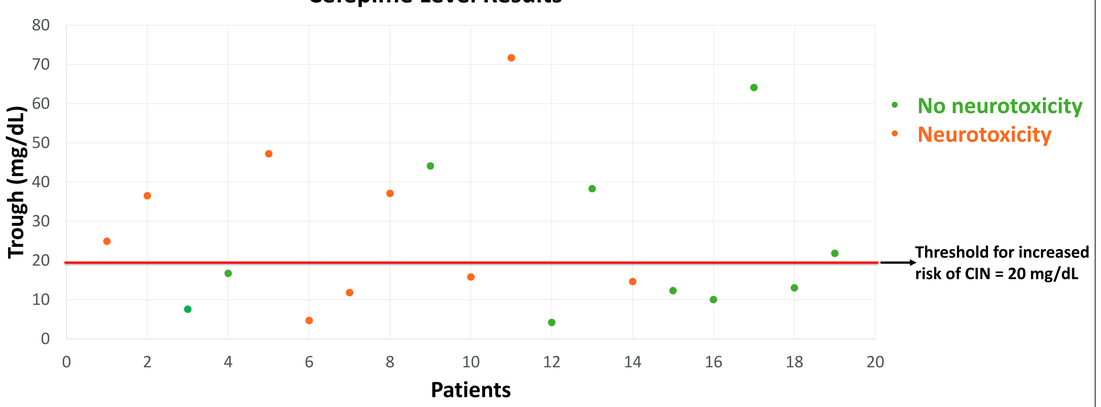
Characteristics (n=20)	n(%), unless otherwise noted
Age, y (median, IQR)	69.5 (61 – 80.5)
Male	12 (60%)
ICU Status	8 (40%)
Baseline SCr, mg/dL (median, IQR)	1.00 (0.50 – 1.20)
SCr at Time of Trough, mg/dL (median, IQR)	1.65 (0.82 – 2.88)
Cefepime Daily Dose at Trough, g/d (median, IQR)	3.5 (1.5 – 4)
Cefepime Duration at Trough, d (median, IQR)	5 (3.5 – 7)
Criteria for Eligibility	
Renal impairment (AKI, CKD, HD, CRRT)	15 (75%)
Signs of neurotoxicity	10 (50%)
Neurotoxic medications	4 (20%)
Pre-existing CNS disease	5 (25%)
Confirm therapeutic dosing	1 (5%)

*Patients may have multiple risk factors for CIN and multiple indications for cefepime

Results

Outcomes	n (%)	p-value	OR or RD% (95% CI)
Primary outcome (n=20)			
Primary analysis			
Trough level ≥ 20 mg/dL	10 (50%)		
Trough level, mg/dL (median, IQR)	19 (12 – 41)		
Renal dose adjustment (n=10)	7 (70%)	0.51	RD -0.30 (-0.65, 0.21)
Cefepime ≥ 4 grams/day for ≥ 4 days (n=4)	2 (50%)	1.00	OR 1.00 (0.11, 8.95)
Renal impairment (n=15)	10 (67%)	0.0325	RD 0.67 (0.13, 0.89)
Signs of neurotoxicity (n=10)	6 (60%)	0.66	OR 2.25 (0.38, 13.47)
Concomitant neurotoxic medications (n=4)	3 (75%)	0.58	OR 0.26 (0.02, 3.06)
Pre-existing CNS disease (n=1)	1 (100%)	1.00	RD 0.53 (-0.48, 0.82)
Secondary outcome			
Intervention confirmed by trough (n=16)	12 (75%)	-	-
Further intervention due to trough (n=19)	6 (32%)	-	-

Cefepime Level Results*



*Cefepime levels were sent to Atlantic Diagnostic Laboratories (uses liquid chromatography with tandem mass spectrometry)

Statistical Analysis

- Descriptive statistics were calculated for baseline characteristics
- Fisher's exact tests were used to calculate p-values for the association between each risk factor for CIN and trough levels ≥ 20 mg/dL
- Odds ratios and risk differences were calculated with contingency table methods for each risk factor for CIN

Limitations

- Small sample size
- Multifactorial etiology of neurotoxicity
- Delayed turnaround time for trough results (1-3 days)
- Inappropriate timing of troughs

Conclusions

- Risk of neurotoxicity increases with increasing cefepime trough levels; may occur with levels < 20 mg/dL
- Renal impairment is a significant risk factor for neurotoxicity, even with renal dose-adjustments; these patients may benefit from cefepime TDM
- TDM allowed for confirmation of interventions made to the antibiotic regimen and for further interventions to be determined

Disclosures

The authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.

Acknowledgements

Aya Haghamad, PharmD, Senior Pharmacist in the Department of Pathology Informatics; directors and managers of Northwell Health Labs, Jeanne Balzano-Kane, MS and Stephanie Epstein, BS, MT(ASCP); Disha Shahani, MPH, Assistant Biostatistician; Nina Kohn, MBA, MA, Project Manager/Senior Biostatistician

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