Massachusetts General Hospital
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HARVARD MEDICAL SCHOOL
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Evaluation of the Carbapenem-Valproate Interaction

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Introduction

- Carbapenem use is increasing with rising antimicrobial resistance rates[1]
- Proposed interaction mechanisms:[2-3]
  - Valproic acid (VPA) transporters and enzymes throughout the intestines and liver may be altered by carbapenems by eradicating enteric enzyme-producing bacteria
  - VPA demonstrates efflux from erythrocytes to the plasma via transporters that may be susceptible to carbapenem inhibition
- Patients taking VPA who are placed on a carbapenem are vulnerable to significantly decreased serum concentrations of valproic acid as early as within 24 hours of use which may result in seizures or behavioral events while subtherapeutic VPA concentrations may last for several weeks after exposure[3]
- The clinical consequences and subsequent therapeutic alterations have not been extensively described[4-6]

Methods

- Retrospective chart review
- January 2017 - June 2022
- Each hospital visit recorded as distinct encounter
- Patients taking VPA for seizures were analyzed separately from those taking for mood stabilization
- Data points collected and recorded using Research Electronic Data Capture (REDCap®)
- Analysis performed with SPSS software version 28
- A waiver of informed consent was granted by the institutional review board (Protocol #: 2022P002184)

Inclusion Criteria

- Hospitalized adult patients (≥ 18 years) at Massachusetts General Hospital and Brigham and Women's Hospital
- Concomitant administration of any carbapenem and a valproate product within 24 hours of each other

Exclusion Criteria

- Administration of other agents known to decrease valproate serum concentrations
- Lack of prolonged exposure to VPA prior to hospitalization (< 30 days)
- Lack of VPA levels drawn both before and after carbapenem initiation
- Admitting diagnosis of seizure or a documented seizure during the hospitalization prior to carbapenem initiation

Primary Outcomes:

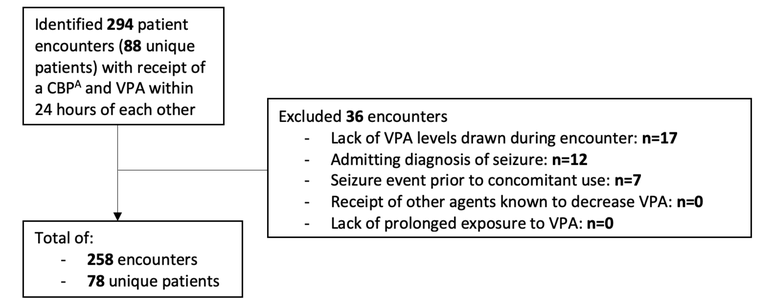
- Incidence of seizures in the seizure control cohort
- Behavioral-related events in the mood-related disorder cohort

Secondary Outcomes:

- Change in total VPA serum concentration
- Time to seizure or behavioral event following the first carbapenem dose
- Incidence of starting a new antiepileptic agent
- Duration of VPA serum concentrations less than 50 mcg/mL
- Incidence of valproate dose increases

Results

Figure 1: Enrollment

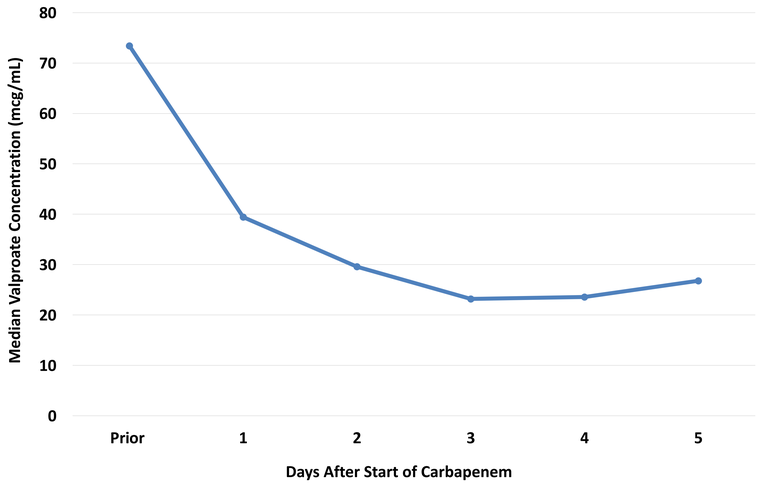


A: Carbapenem

Table 1: Baseline Characteristics

Patient Characteristics (N=78 Patients)	
Age in years - median (IQR)	54 (40-75)
Weight in kilograms - median (IQR)	78.4 (67-91)
Male sex - n (%)	44 (56.4)
VPA indication - n (%)	
Seizure disorder	41 (52.6)
Mood-related disorder	37 (47.4)
Encounter Characteristics (N=258 Encounters)	
Admitting diagnosis - n (%)	
Infectious diseases	96 (37.2)
Neurological	66 (25.6)
Cardiovascular	61 (23.6)
Pulmonary	18 (7.0)
Oncologic	10 (3.9)
Gastrointestinal/genitourinary	7 (2.7)

Figure 2: Change in Valproate Concentration in Valproate-for-Seizure Group (n=134 Encounters)



Therapeutic VPA concentration: 50-100 mcg/mL

Table 2: Outcome Results

VPA for Seizure Control (N=134 Encounters)	
Seizure - n (%)	62 (46.3)
VPA level < 50 mcg/mL - n (%)[A]	44 (71.0)
Median time to event in days (IQR)	2.6 (1.6-5.4)
Median % change in VPA mcg/mL (IQR)	62 (54.9-82.1)
0-24 hours	46.3 (38.4-54.8)
24-48 hours	59.7 (47.6-65.7)
48-72 hours	68.4 (62.3-75.6)
Median duration of VPA concentration < 50 mcg/mL in days (IQR)	8.9 (4.8-14.9)
Addition of new AED[B] - n (%)	32 (23.9)
VPA dose increase - n (%)	41 (30.6)
Median % dose increase (IQR)	50 (35-75)
VPA for Mood-Related Disorder (N=124 Encounters)	
Behavioral disturbance - n (%)	63 (50.8)
Psychiatric consult ordered[C]	38 (60.3)
Keyword identified[C]	25 (39.7)
Median time to event in days (IQR)	5.2 (2.6-7.6)
VPA dose increase - n (%)	40 (32.3)

A: Represented as n (%) in those with seizure
B: Antiepileptic drug
C: Represented as n (%) in those with a behavioral disturbance

Table 3: Primary Outcome Compared Amongst Carbapenems

Outcome	Meropenem (N=126 Encounters)	Ertapenem (n=66 Encounters)	Imipenem-cilastatin (N=55 Encounters)
Seizure or behavioral disturbance - n (%)	65 (51.6)	27 (40.9)	33 (60)

Conclusions

- 46.3% of encounters in the seizure control cohort experienced seizures following carbapenem use
  - 71% of encounters with seizures were characterized by subtherapeutic VPA concentrations
- 50.8% of patients taking VPA for mood-related disorders experienced a behavioral disturbance
- VPA concentrations decreased rapidly within the first 24 hours of initiation
- Clinicians should be aware of this interaction and alternative antimicrobial agents should be considered whenever possible
- Future studies are warranted to determine the efficacy of the varying strategies utilized to avoid or overcome this drug-drug interaction

References

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