On Shaky Grounds: Carbapenem Use with Concomitant Seizure Disorders and Valproic Acid

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Outline

- Case
- Background
- Clinical Questions
- Review of Evidence
- Recommendation
- Monitoring
- Follow-Up

Learning Objectives

- To review the evidence behind carbapenem use with concomitant seizure disorders
- To understand the proposed mechanisms and clinical significance of the drug-drug interaction between meropenem and valproic acid

Case

- ID: MH, 21 yo quadriplegic male, 75kg
- Brought to VGH ER Nov. 7 from George Pearson Centre (GPC)
- CC: Suprapubic pain
- HPI:
  - Increasing suprapubic pain, gross hematuria, fever, chills over past 2 days
  - Brought to ER from GPC

Case

- PMH:
  - C2/C3 quad 2º to GSW 2006, ventilator-dependent
  - Partial motor and myoclonic sz disorder 2º to anoxic brain injury from GSW
    - Complicated history, ++ neurology consults, many trials of different medications
- SH:
  - Now lives at GPC subsequent to injury
- Allergies
  - Latex
  - Moxifloxacin (reaction: hepatitis)

Case

- Medications PTA (at GPC):
  - **Divalproex 250mg bid, 500mg qhs**
  - **Levetiracetam 1500mg bid**
  - **Clonazepam 1mg tid**
  - **Pregabalin 150mg bid**
  - Oxybutnin 5mg bid
  - Buspirone 5mg bid (anxiety)
  - Multivitamin daily
  - Methylcellulose 1% ou i drop bid
  - Ciprofloxacin 500mg bid started Nov. 7

Case

- PRN Medications PTA:
  - Dimenhydrinate 50mg im qid
  - Acetaminophen 650mg qid
  - Docusate 100mg q2h
  - Lorazepam 0.5-1mg q4h

Review of Systems at Admission

- Vitals:
  - T 38.2, HR 95, BP 120/55 RR 16 SpO_2 93%
- CNS: GCS 15, unremarkable
- CVS: MAP = 70, unremarkable
- Resp: On A/C ventilation
- GI:Able to swallow, unremarkable
- GU:
  - U/O 30-40ml/hr, hematuria
  - increasing suprapubic pain

Review of Systems on Admission

- Labs:

Parameter	Nov. 7	Nov. 8
WBC (4-11)	5.8	**36.1**
Hb (135-180)	149	**111**
Plt (150-400)	**82**	**101**
INR (0.9-1.2)	1.1	1.1
SrCr (30-130)	54	36
Na (135-145)	138	**146**
K (3.5-5.0)	3.6	**2.9**

ICU Admission

- Patient admitted to ICU Nov. 9 (0400) for sepsis (suspected urosepsis) and query VAP/HCAP
- Started on broad-spectrum antibiotics
- Drew blood, respiratory, and urine cultures

Review of Systems on Admission

- Cultures:

Date	Site	Organism(s)	Sensitivity	Resistance
N7	Urine	Negative		
N7	Resp	Staph aureus	MSSA	Pen G
N8	Blood	Serratia marascens	Ceftriax/Cipro/Gent/Imi/ Septra	Cefaz
		Group B H. Strep	Ceftriax/Pen G/Vanco	
		E. coli	Cefaz/Gent/Imi/Septra/ PipTaz	**Cipro**
		E. aerogenes	Ceftriax/Imi/Gent	Cefaz/**Cipro**/**Septra**/ **PipTaz(Intermediate)**
		Proteus mirabilis	Cipro/Ceftriax/Septra/PipTaz /Gent/Imi	Cephalex(Intermediate)
N10	Resp	Mixed GNB incl. Pseudomonas	No sensitivities given	

Initial Medications in ICU

- Divalproex 250mg bid, 500mg qhs
- Levetiracetam 1500mg bid
- Pregabalin 150mg bid
- Folic acid 5mg, Thiamine 100mg, Multivitamin daily x 3 days
- Heparin 5000U sc q12h
- Ranitidine 150mg po bid
- Ipratroprium 250-500 ug q6h neb
- Salbutamol 2.5-5mg q6h neb
- **Meropenem 1g iv q8h**
- **Vancomycin 1g q12h**

Pharmacy called regarding interaction

Case Drug-Related Problems

- **MH is at risk of experiencing a seizure secondary to receiving a carbapenem antibiotic and would benefit from reassessment of his antibiotic therapy**
- **MH is at risk of experiencing a seizure secondary to a drug-drug interaction between meropenem and valproic acid and would benefit from reassessment of his antibiotic drug therapy**
- MH is at risk of experiencing nephrotoxicity and ototoxicity secondary to receiving vancomycin without an appropriate initial assessment of renal function, and would benefit from monitoring of his vancomycin levels
- MH is at risk of experiencing a seizure secondary to not receiving clonazepam, and would benefit from receiving this drug
- MH is at risk of experiencing anxiety secondary to not receiving buspirone, and would benefit from receiving this drug

Goals of Therapy

- Resolve sepsis
- Treat infection
  - Address underlying cause
- Prevent reoccurrence of seizures
- Reduce mortality

Background - Drugs

- Meropenem
  - MOA: Bactericidal, time-dependent killing broad-spectrum β-lactam antibiotic, inhibits cell-wall synthesis
  - PK
    - A: Tmax ~1hr after infusion
    - D: Protein binding ~2%, Vd 12-20L, %CSF/Blood = 2-12
    - M: Extrarenally 20-25%
    - E: Cleared renally as 70% unchanged drug. T1/2 = 1hr, but can be 3.4-20hrs in renal dysfunction
  - Usual dose: 1gm iv q8h

Creatinine Clearance (mL/min)	>50	26-50	10-25	<10
Dose	1g q8h	1gq12h	500mg q12h	500mg q24h

Background - Drugs

- Valproic Acid
  - MOA: Mood stabilizer and anti-epileptic. MOA not completely understood, thought to be related to elevated GABA in brain
  - Usual dose: 500-1500mg/day divided od-tid
  - Therapeutic range: 350-700 umol/L
  - PK:
    - A: F = 80-90% depending on fasting state
    - D: Vd = 11L/1.73m^2

      Protein binding ~90%, concentration-dependent
    - M: Hepatic via conjugation (glucuronidation)
    - E: Cleared renally 70-80% as glucuronide metabolite, <3% unchanged

      T1/2 = 9-16hr

Clinical Question 1

- Does imipenem predispose patients to a higher seizure risk than meropenem?

Carbapenems and Seizure Induction

- Proposed mechanisms:
  - Mutlifactorial, includes:
    - Ability to block $GABA_A$ receptor
    - Action on other neuroreceptor complexes
- β-lactams are the most common antibiotic class associated with seizures
- Cilastatin alone has not been shown to produce seizures

Literature Search

- Databases searched:
  - Pubmed, Embase, MedLine, Google Scholar, and bibliographies of relevant articles
- Search terms:
  - Meropenem, imipenem, carbapenems, seizure, risk, safety
- Found:
  - 1 systematic review, discussing:
    - 3 RCTs
    - 1 prospective uncontrolled study
    - 4 retrospective analyses
    - Multiple case reports

Safety of Imipenem/Cilastatin in Neurocritical Care Patients

Hoffmann et al

Neurocrit Care 2009;10:403-7

Systematic Review

- Hoffman et al. (2007)

Study Type	Excluded Sz Dx?	Imipenem	Meropenem
		Seizures/All patients (%)	Seizures/All patients (%)
RCT 1	Yes	1/91	0/87
RCT 2	Yes	0/98	0/106
RCT 3	Yes	2/75	2/76
RR (‘88)	No	52/1754	
RR (‘99)	Yes	10/1802	22/4748
RR (‘99)	Yes	10/1375	19/2790
PS (‘93)	No	4/1951	
Total		79/7146 (1.1%)	43/7807 (0.55%)

RR = Retrospective Review, PS = Prospective Study

Limitations

- Review article
- Summarizing safety data - low level of evidence
- Most of the studies exclude patients with seizure disorders
- Some studies simply use “adverse events” as a blanket term

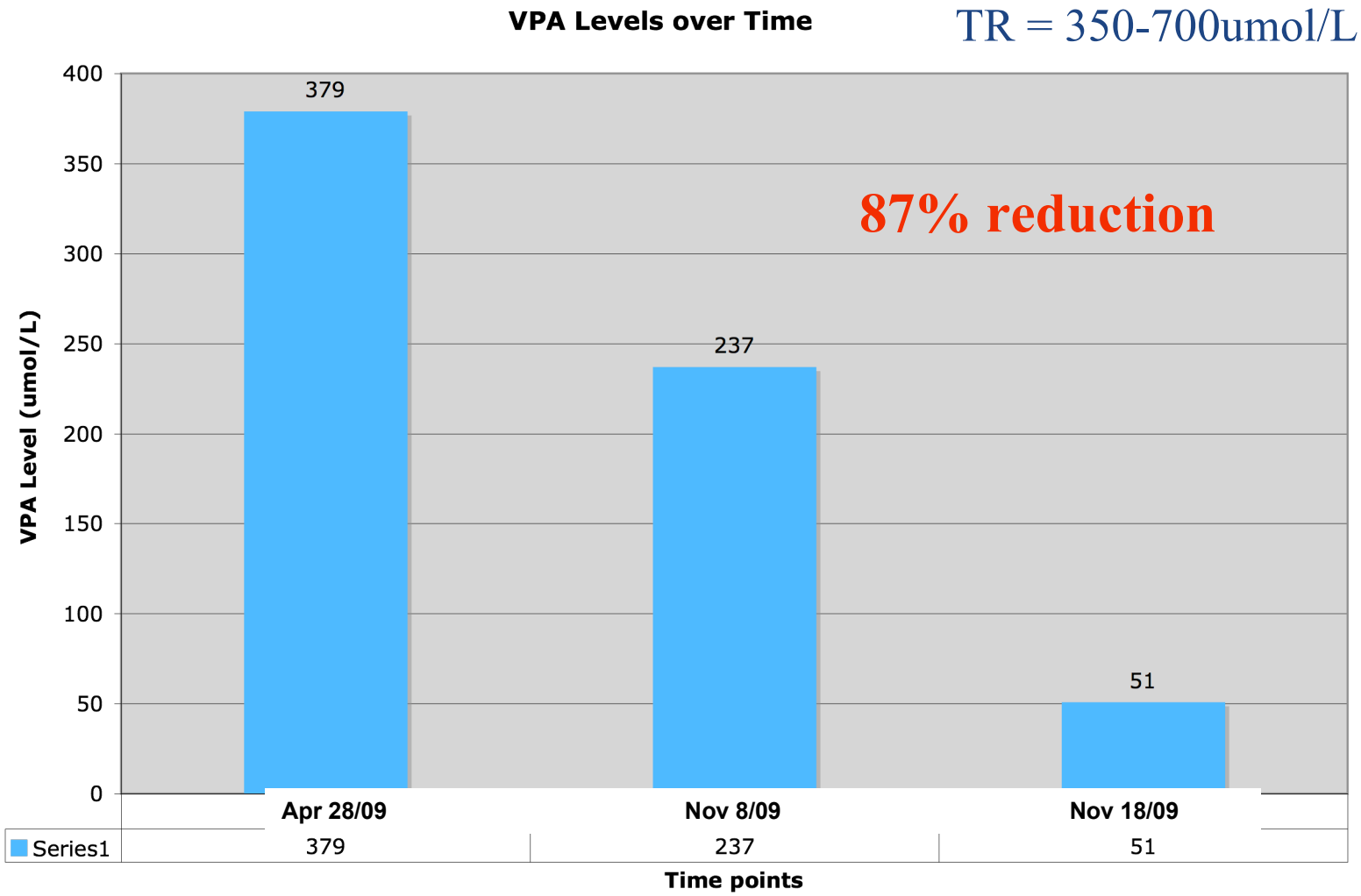
Back to Clinical Question 1

- Cannot conclude from available data whether imipenem actually predisposes patients to a higher risk of seizures than meropenem
- Risk factors for imipenem-induced seizures are:
  - Low weight
  - Renally impaired
  - Non-adjusted doses for renal function
- Using meropenem over imipenem in pts with seizure disorders may be safer
- Cost is similar ($97.52 Imi vs $146.1 Mero per day)

Back to Case - Nov. 18

- MH is still receiving meropenem 1g iv q8h for a polymicrobial bacteremia
- Plan is for a two-week course (Nov. 8-22)
- VPA level ordered for Nov. 18 because of suspicion of interaction
  - Level on Nov. 8 was 237umol/L, but pt had missed 3 previous doses due to ER admission
  - Pt had a previous steady-state level from a previous admission

VPA Levels



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Clinical Question 2

- Does meropenem cause a reduction in valproic acid levels, and what is the clinical significance of this interaction?

Meropenem-Valproic Acid Interaction

- Proposed mechanism:
  - Carbapenems increase UDP-GA levels, thus enhancing VPA glucuronidation
- Other, less supported mechanisms:
  - Increased renal clearance of VPA-Glu
  - Increased VPA uptake into erythrocytes

Literature Search

- Databases searched:
  - Pubmed, Embase, MedLine, Google Scholar, and bibliographies of relevant articles
- Search terms:
  - Meropenem, imipenem, carbapenems, valproic acid, interaction
- Found:
  - 1 retrospective study
  - 13 case reports

Interaction Between Valproate and Meropenem: A Retrospective Study

Spriet et al

Ann Pharmacother 2007;1130-6

Meropenem-VPA Interaction

- Spriet et al. (2007)
  - Retrospective 18-month chart review (Jan 2004 -June 2005)
  - Assessed patients who received both meropenem and valproic acid
  - Obtained clinical records, lab results, EEG recordings, demographics, and medications (including doses, durations and indications)
  - Outcomes included:
    - PK interaction (valproic acid levels)
    - Clinical interaction (increased EEG epileptic discharges, and/or clinical deterioration of seizure activity)

Meropenem-VPA Interaction

- Spriet et al. (2007)
  - Results:
    - 39 patients met inclusion criteria in study period
    - Mean daily valproic acid dose = 1.6 ± 0.68g
    - Mean daily meropenem dose = 2.67 ± 1.4g

We saw an 87% decrease

	Mean VPA Level (umol/L)		Decrease
	Pre-combo	During combo	
VPA, then Mero (n=29)	446 ± 146	156 ± 83	66 ± 17%
Mero, then VPA (n=10)	N/A	81.8 ± 69	

Meropenem-VPA Interaction

- Spriet et al. (2007)
  - Results:
    - Chronicity:
      - VPA levels dropped within 24 hours of combination
      - Levels took, on average, 8 days to become therapeutic again
    - Data were only sufficient to assess clinical relevance of the interaction in 20 patients:
      - **11/20** patients showed electroclinical deterioration:
        - » 9/20 experienced increased seizure activity
        - » 7/20 showed increased epileptic discharges
        - » 5/20 showed increase in both outcomes

Limitations

- Retrospective design
- Lack of control subjects
- Free VPA levels were not assessed
- Methodology a bit unclear
- Insufficient data to evaluate all eligible patients
  - EEG recordings, clinical disease progression, recordings of seizures

Summary of Case Reports

Table 1. Overview of Published Case Reports

Reference	Pt. Age, y	Daily VPA Dose	Type of Carbapenem	Interaction Duration, d	Effect on VPA Concentration, %	Outcome
Nagai (1997)[2]	10	8.3 mg/kg tid	panipenem	8	–93.5	seizures on day 13
	8	500 mg	panipenem	10	–95	no acute seizures
De Turck (1998)[3]	65	1200 mg	meropenem	switch PHT	not known	seizures on day 2
	57	not known	meropenem	not known	–60	no acute seizures
Yamagata (1998)[4]	3	35 mg/kg/day	panipenem	1	–65	seizures on day 3
	22	32 mg/kg/day	panipenem	12	–76	seizures on day 2
	4	25 mg/kg/day	panipenem	not known	–58.5	no acute seizures
Llinares (2003)[5]	28	1600 mg	imipenem	not known	–70	no acute seizures
	71	1500 mg	meropenem	not known	–75	seizures on day 9
	24	1600 mg	meropenem	not known	not known	no acute seizures
Nacarkucuk (2004)[6]	14	50 mg/kg/day	meropenem	7	–47.5	no acute seizures
	7 mo	75 mg/kg/day	meropenem	3	–75.5	no acute seizures
	14 mo	75 mg/kg/day	meropenem	3	–84.7	no acute seizures
Clause (2005)[7]	30	3600 mg/day	meropenem	not known	–72	no acute seizures
	77	24 mg/kg/day	meropenem	not known	not known	no acute seizures
Coves-Orts (2005)[8]	21	1000 mg	meropenem	5	–20.1	seizures on day 2
Lam (2005)[9]	21	1920 mg	meropenem	not known	not known	myoclonia on day 2
Santucci (2005)[10]	9.5	600 mg	meropenem	not known	–64	seizures on day 5
Perea-Falomir (2006)[11]	46	1200 mg	imipenem	not known	not applicable	seizures on day s 1 and 2
Cabanes-Mariscal (2006)[12]	80	1100 mg	ertapenem	not known	–49	no acute seizures
Fudio (2006)[13]	50	2750 mg	meropenem	17	–85	myoclonia on day 5
Spriet (2007)[14]	60	32 mg/kg/day	meropenem	not known	–65	no acute seizures
	54	28 mg/kg/day	meropenem	not known	–56	no acute seizures

PB = phenobarbital; PHT = phenytoin; VPA = valproate.

Back to Clinical Question 2

- Evidence available makes it hard to come to a definitive conclusion
- Pharmacokinetic interaction exists
- Clinically significant interaction is definitely possible; however, actual incidence and severity is unknown
- In the interest of safety, it is reasonable to avoid concurrent administration of VPA and meropenem

Recommendation

- Increase valproic acid dose to 500mg tid for 4 days
- Maintain meropenem for course of therapy as per polymicrobial, multi-drug resistant infection
  - Source of infection still unclear
- Reduce valproic acid dose back to 250mg bid, 500mg qhs Nov. 26

Monitoring

Outcome	Observation	Timeline	By Who
Seizures	Myoclonic activity, facial jerks	Daily	Nurse, Physician
Infxn eradication	Negative blood cultures, T, WBC, HD stability	Nov. 22	Physician, Pharmacist
VPA SE's	Drowsiness, rash, headache, N/V/D	Daily	Physician, Pharmacist
VPA Levels	Return to therapeutic range	1 week	Physician, Pharmacist
ICU discharge	Hemodynamic stabilization	Daily	Physician, Nurse

What Actually Happened

- VPA dose was increased to 500mg tid (1000mg/day to 1500mg/day)
- Meropenem dose was maintained for duration of antibiotic therapy (until Nov. 22)
- No seizures were noted during meropenem therapy
- Patient was discharged back to GPC Nov. 22
  - VPA dose was **recommended to be** decreased back to baseline shortly after discharge

Conclusion

On day 50, administration of MEPM was stopped on the advice of the Clinical Pharmacology Service. The last episode of seizures was reported that day.

- As pharmacists, we can play a role in preventing seizures by being aware of this interaction

References

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Questions?

RCT - Verwaest et al (1999)

- Method: Multicenter, open-label RCT
- Intervention: Imipenem/Cilastatin 1g q8h
- Comparator: Meropenem 1g q8h
- Population: 212 ICU pts with presumed LRTI, IAI, or sepsis (empiric therapy)
- Outcomes: % of pts with satisfactory response
- Results: 77% Mero vs 68.1% Imi (p=0.185)
- Seizures: Excluded CNS conditions, **1 seizure with imipenem/cilastatin**

RCT - Colardyn et al (1996)

- Multicentre, open-label, Ran. Phase III trial
- Hospitalized pts requiring iv abx for serious infxns (IAI, SSTI, LRTI, UTI, sepsis)
- Meropenem vs. Imipenem 1g iv q8h
- N=204, Outcome = % clinical response
- 76% Mero vs 77% Imipenem (no p value)
- **Safety was assessed, but no mention of seizures**

RCT - Garau et al (1997)

- Multicentre, open-label RCT
- Pts requiring iv abx for serious infxns (various)
- Meropenem vs Imipenem 1g q8h
- N = 151, excluded seizure disorders
- Outcome = clinical response rate per infxn
- 87% Meropenem vs. 74% Imipenem (NSS)
- **2 seizures in meropenem group, 2 seizures in imipenem group**

Summary of Patients with Interaction

Table 3. Clinical Correlations in Patients with Electroclinical Deterioration

Correlation	Pt. 1	Pt. 2	Pt. 3	Pt. 4	Pt. 5	Pt. 6	Pt. 7	Pt. 8	Pt. 9	Pt. 10	Pt. 11
VPA level before start of MPN	119	61	NA	NA	42	NA	61	41	NA	84	65
VPA level after start of MPN	34	23	7	5	21	20	21	4	37	41	26
Neurologic status before MPN–VPA	no seizures	SSE	SSE	GTCS + SSE	CPSE	coma	SSE	no seizures	coma	SSE	SSE
Neurologic status during MPN–VPA	↑↑ seizures	SSE	SSE	SSE	CPSE	coma	SSE, ↑ myoclonic jerks	GTCS	coma	SSE	SSE, ↑ blinking + tonic eye deviation
Neurologic status after MPN–VPA	↓ seizures	↓ blinking	↓ blinking	↑ conscious	↑ conscious	↑ conscious	↑ conscious	no seizures	coma	SSE	↑ conscious
EEG before MPN–VPA	no EEG	BR 3 E +	BR 1 E –	BR 1 E –	BR 2 E +	BR 2 E + (SE)	BR 1 E –	BR 2 E –	BR 2 E +	BR 1 E –	burst suppression, E +
EEG during MPN–VPA	no EEG	BR 3 E ↑	BR 1 E +	BR 1 E –	BR 2 E ↑	BR 2 E ↑ (SE)	BR 1 E –	BR 2 E –	BR 2 E ↑	BR 2 E +	burst suppression, E ↑↑
EEG after MPN–VPA	no EEG	BR 3 E –	BR 1 E –	BR 1 E –	BR 2 E –	BR 2 E –	BR 1 E –	BR 2 E –	BR 2 E –	BR 3 E –	BR 2 E ↓

BR = background rhythm (1 = severely slowed, 2 = moderately slowed, 3 = mildly slowed); CPSE = complex partial status epilepticus; E = epileptic discharges (+ = present, – = absent, ↑ = increase, ↓ = decrease); EEG = electroencephalogram; GTCS = generalized tonic-clonic seizure; MPN = meropenem; NA = not applicable; SE = status epilepticus; SSE = subtle status epilepticus; VPA = valproate.