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
  - Oxybutynin 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 SpO₂ 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:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nov. 7</th>
<th>Nov. 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (4-11)</td>
<td>5.8</td>
<td>36.1</td>
</tr>
<tr>
<td>Hb (135-180)</td>
<td>149</td>
<td>111</td>
</tr>
<tr>
<td>Plt (150-400)</td>
<td>82</td>
<td>101</td>
</tr>
<tr>
<td>INR (0.9-1.2)</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>SrCr (30-130)</td>
<td>54</td>
<td>36</td>
</tr>
<tr>
<td>Na (135-145)</td>
<td>138</td>
<td>146</td>
</tr>
<tr>
<td>K (3.5-5.0)</td>
<td>3.6</td>
<td>2.9</td>
</tr>
</tbody>
</table>
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:

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

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>&gt;50</th>
<th>26-50</th>
<th>10-25</th>
<th>&lt;10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>1g q8h</td>
<td>1gq12h</td>
<td>500mg q12h</td>
<td>500mg q24h</td>
</tr>
</tbody>
</table>
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/1.73m²
      - 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<sub>A</sub> 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)

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

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
• 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)
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

VPA Levels over Time

TR = 350-700umol/L

87% reduction

Pharmacy Services
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

<table>
<thead>
<tr>
<th></th>
<th>Mean VPA Level (umol/L)</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-combo</td>
<td>During combo</td>
</tr>
<tr>
<td>VPA, then Mero (n=29)</td>
<td>446 ± 146</td>
<td>156 ± 83</td>
</tr>
<tr>
<td>Mero, then VPA (n=10)</td>
<td>N/A</td>
<td>81.8 ± 69</td>
</tr>
</tbody>
</table>
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>
<thead>
<tr>
<th>Reference</th>
<th>Pt. Age, y</th>
<th>Daily VPA Dose</th>
<th>Type of Carbapenem</th>
<th>Interaction Duration, d</th>
<th>Effect on VPA Concentration, %</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nagai (1997)²</td>
<td>10</td>
<td>8.3 mg/kg tid</td>
<td>panipenem</td>
<td>8</td>
<td>-93.5</td>
<td>seizures on day 13</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>500 mg</td>
<td>panipenem</td>
<td>10</td>
<td>-95</td>
<td>no acute seizures</td>
</tr>
<tr>
<td>De Turck (1998)³</td>
<td>65</td>
<td>1200 mg</td>
<td>meropenem</td>
<td>switch PHT</td>
<td>not known</td>
<td>seizures on day 2</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>not known</td>
<td>meropenem</td>
<td>not known</td>
<td>-60</td>
<td>no acute seizures</td>
</tr>
<tr>
<td>Yamagata (1998)⁴</td>
<td>3</td>
<td>35 mg/kg/day</td>
<td>panipenem</td>
<td>1</td>
<td>-65</td>
<td>seizures on day 3</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>32 mg/kg/day</td>
<td>panipenem</td>
<td>12</td>
<td>-76</td>
<td>seizures on day 2</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>25 mg/kg/day</td>
<td>panipenem</td>
<td>not known</td>
<td>-58.5</td>
<td>no acute seizures</td>
</tr>
<tr>
<td>Llinares (2003)⁶</td>
<td>28</td>
<td>1600 mg</td>
<td>imipenem</td>
<td>not known</td>
<td>-70</td>
<td>no acute seizures</td>
</tr>
<tr>
<td></td>
<td>71</td>
<td>1500 mg</td>
<td>meropenem</td>
<td>not known</td>
<td>-75</td>
<td>seizures on day 9</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>1600 mg</td>
<td>meropenem</td>
<td>not known</td>
<td>not known</td>
<td>no acute seizures</td>
</tr>
<tr>
<td>Nacarkucuk (2004)⁶</td>
<td>14</td>
<td>50 mg/kg/day</td>
<td>meropenem</td>
<td>7</td>
<td>-47.5</td>
<td>no acute seizures</td>
</tr>
<tr>
<td></td>
<td>7 mo</td>
<td>75 mg/kg/day</td>
<td>meropenem</td>
<td>3</td>
<td>-75.5</td>
<td>no acute seizures</td>
</tr>
<tr>
<td></td>
<td>14 mo</td>
<td>75 mg/kg/day</td>
<td>meropenem</td>
<td>3</td>
<td>-84.7</td>
<td>no acute seizures</td>
</tr>
<tr>
<td>Clause (2005)⁷</td>
<td>30</td>
<td>3600 mg/day</td>
<td>meropenem</td>
<td>not known</td>
<td>not known</td>
<td>no acute seizures</td>
</tr>
<tr>
<td></td>
<td>77</td>
<td>24 mg/kg/day</td>
<td>meropenem</td>
<td>not known</td>
<td>not known</td>
<td>no acute seizures</td>
</tr>
<tr>
<td>Coves-Orts (2005)⁸</td>
<td>21</td>
<td>1000 mg</td>
<td>meropenem</td>
<td>5</td>
<td>-20.1</td>
<td>seizures on day 2</td>
</tr>
<tr>
<td>Lam (2005)⁹</td>
<td>21</td>
<td>1920 mg</td>
<td>meropenem</td>
<td>not known</td>
<td>not known</td>
<td>myoclonia on day 2</td>
</tr>
<tr>
<td>Santucci (2005)¹⁰</td>
<td>9.5</td>
<td>600 mg</td>
<td>meropenem</td>
<td>not known</td>
<td>-64</td>
<td>seizures on day 5</td>
</tr>
<tr>
<td>Perea-Falomir (2006)¹¹</td>
<td>46</td>
<td>1200 mg</td>
<td>imipenem</td>
<td>not known</td>
<td>not applicable</td>
<td>seizures on day 1 and 2</td>
</tr>
<tr>
<td>Cabanes-Mariscal (2006)¹²</td>
<td>80</td>
<td>1100 mg</td>
<td>ertapenem</td>
<td>not known</td>
<td>-49</td>
<td>no acute seizures</td>
</tr>
<tr>
<td>Fudio (2006)¹³</td>
<td>50</td>
<td>2750 mg</td>
<td>meropenem</td>
<td>17</td>
<td>-85</td>
<td>myoclonia on day 5</td>
</tr>
<tr>
<td>Spriet (2007)¹⁴</td>
<td>60</td>
<td>32 mg/kg/day</td>
<td>meropenem</td>
<td>not known</td>
<td>-65</td>
<td>no acute seizures</td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>28 mg/kg/day</td>
<td>meropenem</td>
<td>not known</td>
<td>-56</td>
<td>no acute seizures</td>
</tr>
</tbody>
</table>

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

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


Questions?

- 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

- 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

<table>
<thead>
<tr>
<th>Correlation</th>
<th>Pt. 1</th>
<th>Pt. 2</th>
<th>Pt. 3</th>
<th>Pt. 4</th>
<th>Pt. 5</th>
<th>Pt. 6</th>
<th>Pt. 7</th>
<th>Pt. 8</th>
<th>Pt. 9</th>
<th>Pt. 10</th>
<th>Pt. 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPA level before start of MPN</td>
<td>119</td>
<td>61</td>
<td>NA</td>
<td>NA</td>
<td>42</td>
<td>NA</td>
<td>61</td>
<td>41</td>
<td>NA</td>
<td>84</td>
<td>65</td>
</tr>
<tr>
<td>VPA level after start of MPN</td>
<td>34</td>
<td>23</td>
<td>7</td>
<td>5</td>
<td>21</td>
<td>20</td>
<td>21</td>
<td>4</td>
<td>37</td>
<td>41</td>
<td>26</td>
</tr>
<tr>
<td>Neurologic status before MPN–VPA</td>
<td>no sei-</td>
<td>SSE</td>
<td>SSE</td>
<td>GTCS +</td>
<td>CPSE</td>
<td>coma</td>
<td>SSE</td>
<td>no sei-</td>
<td>coma</td>
<td>SSE</td>
<td>SSE</td>
</tr>
<tr>
<td>Neurologic status during MPN–VPA</td>
<td>↑↑ sei-</td>
<td>SSE</td>
<td>SSE</td>
<td>SSE</td>
<td>CPSE</td>
<td>coma</td>
<td>SSE</td>
<td>↑ myoclonic</td>
<td>GTCS</td>
<td>coma</td>
<td>SSE</td>
</tr>
<tr>
<td>Neurologic status after MPN–VPA</td>
<td>↓ sei-</td>
<td>↓ blinking</td>
<td>↓ blinking</td>
<td>↑ conscious</td>
<td>↑ conscious</td>
<td>↑ conscious</td>
<td>↑ conscious</td>
<td>no sei-</td>
<td>coma</td>
<td>SSE</td>
<td>↑ conscious</td>
</tr>
<tr>
<td>EEG before MPN–VPA</td>
<td>no EEG</td>
<td>BR 3</td>
<td>BR 1</td>
<td>BR 1</td>
<td>BR 2</td>
<td>BR 2</td>
<td>BR 1</td>
<td>BR 2</td>
<td>BR 2</td>
<td>BR 1</td>
<td>burst suppression, E +</td>
</tr>
<tr>
<td>EEG during MPN–VPA</td>
<td>no EEG</td>
<td>BR 3</td>
<td>BR 1</td>
<td>BR 1</td>
<td>BR 2</td>
<td>BR 2</td>
<td>BR 1</td>
<td>BR 2</td>
<td>BR 2</td>
<td>BR 2</td>
<td>burst suppression, E ↑</td>
</tr>
<tr>
<td>EEG after MPN–VPA</td>
<td>no EEG</td>
<td>BR 3</td>
<td>BR 1</td>
<td>BR 1</td>
<td>BR 2</td>
<td>BR 2</td>
<td>BR 1</td>
<td>BR 2</td>
<td>BR 2</td>
<td>BR 3</td>
<td>BR 2</td>
</tr>
</tbody>
</table>

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.