Controversial Role of Ketamine in Treatment of Refractory Status Epilepticus

Senka Runjaic, PharmD
PGY-1 Pharmacy Resident

January 24th, 2015

Disclosure Statement

• The author of this presentation has the following to disclose concerning possible financial or personal relationships with commercial entities that may have direct or indirect interest in the subject matter of this presentation

• Senka Runjaic, PharmD – nothing to disclose

Objectives

• Define status epilepticus (SE) and refractory status epilepticus (RSE)
• Review etiology and pathophysiology of SE
• Explain the role of ketamine for treatment of RSE
• Discuss pharmacists’ role in improving clinical outcomes

Status Epilepticus (SE)

• No consensus on exact definition
• Traditional definition
  – Any seizure lasting longer than 30 min whether or not consciousness is impaired
• Modified definition
  – Five minutes or more of continuous clinical and/or electrographic (EEG) seizure activity or
  – Recurrent seizure activity without recovery (returning to baseline) between seizures

Etiology

<table>
<thead>
<tr>
<th>Acute processes</th>
<th>Chronic processes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>Preceding epilepsy (breakthrough or discontinuation of medications)</td>
</tr>
<tr>
<td>Metabolic disturbance</td>
<td>Chronic ethanol abuse (withdrawal)</td>
</tr>
<tr>
<td>CNS Infection</td>
<td>CNS tumors</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td>Head trauma</td>
<td></td>
</tr>
<tr>
<td>Drug issues (toxicity, withdrawal, non-compliance)</td>
<td></td>
</tr>
<tr>
<td>Hypoxia, cardiac arrest</td>
<td></td>
</tr>
<tr>
<td>Hypertensive encephalopathy</td>
<td></td>
</tr>
<tr>
<td>Autoimmune encephalitis</td>
<td></td>
</tr>
</tbody>
</table>

When Does SE Become Refractory?

“Patient who continues to experience either clinical or EEG seizures after initial doses of an initial benzodiazepine followed by a second acceptable AED will be considered refractory.”
Management of Refractory Status Epilepticus

Time-Dependent Pharmacoresistance

Management of RSE

- If RSE has been established
  Consider repeat bolus of the urgent control AED

- Start continuous infusion (CI) AEDs
  - Midazolam
  - Propofol
  - Barbiturates

Anesthetic Agents for RSE - Midazolam

- **Dose:**
  - LD – 0.2 mg/kg, administer at 2 mg/min
  - CI – 0.05-2 mg/kg/hr

- **Advantages:**
  - Predictable PK/PD profile
  - Availability of antidote (flumazenil)
  - Can be used in combination with propofol

- **Considerations:**
  - Tachyphylaxis
  - Respiratory depression
  - Hypotension

Anesthetic Agents for RSE - Propofol

- **Dose:**
  - Loading dose (LD) – 1-2 mg/kg
  - CI – 30-200 mcg/kg/min

- **Advantages:**
  - Short T1/2, rapid titration/withdrawal
  - Relative safety with prolonged use in ICU patients

- **Considerations:**
  - Propofol infusion syndrome (PRIS)
    - Severe metabolic acidosis
    - Rhabdomyolysis
    - Renal failure; CV collapse

Anesthetic Agents for RSE – Pentobarbital

- **Dose:**
  - LD – 5-15 mg/kg, administer at ≤50 mg/min
  - CI – 0.5-5 mg/kg/h

- **Advantages:**
  - Theoretical neuroprotective effect
  - Efficacy

- **Considerations:**
  - Very long T1/2, prolonged recovery
  - Myriad of drug interactions
  - Profound CV depression
  - Ileus, suppressed immunity
Emerging treatment for RSE - ketamine

- **MOA:**
  - Non-competitive NMDA receptor antagonist
- **Pharmacokinetics:**
  - T1/2 greater than 2.5 hours
  - Vd 3L/kg
  - Metabolism – CYP450, excretion – primarily urine
- **Dosing:**
  - Induction of anesthesia
    - IM: 6.5 to 13 mg/kg
    - IV: 1 to 4.5 mg/kg

Indications:
- FDA labeled
  - General anesthesia
  - Procedural sedation
- Non-FDA labeled
  - Analgesia
  - Bronchospasm
  - Rapid sequence intubation, induction

Major adverse effects:
- Common: BP, HR
- Serious: cardiac dysrhythmias, apnea, respiratory depression

Original Use of Ketamine for RSE

- **1998 case report**
  - Previously healthy 13 y/o girl
  - 3 day h/o muscle aches, fever, and GTC seizures
  - Etiology could not be determined

- **Treatment prior to introduction of ketamine**
  - IV diazepam, CI midazolam
  - LD and CI of phenytoin and phenobarbital
  - Pentobarbital coma x 4 weeks
  - IV lorazepam, lidocaine, and valproate
  - Propofol (bolus followed by CI)

Early Administration of Ketamine in RSE

- **2012 case report**
  - 60 y/o with cerebral palsy and epilepsy
  - Admitted for CAP
  - Developed NCSE
  - Coma, poor airway protection intubation

- **Treatment prior to introduction of ketamine**
  - Escalating doses of midazolam
  - Phenytoin LD
  - Levetiracetam
  - Propofol
  - MAP compromised NE (max 0.26 mcg/kg/min)

- **IV ketamine**
  - 2 mg/kg bolus
    - Controlled seizures after 90 sec
    - CI up to 7.5 mg/kg/hr
    - Remained on ketamine for 14 days

- **Clinical outcome**
  - 24 hours after sedatives weaned off – regained consciousness
  - After 3 weeks of inpatient rehab – complete return to baseline
**Early Administration of Ketamine in RSE**

- Ketamine was used **substantially early**
  - Immediate and sustained efficacy
  - Excellent clinical outcome
  - "Vasopressor-sparing" role

**NMDA Antagonists for RSE - Review**

- **Overview**:
  - Systematic review
  - 20 retrospective case series/reports
  - Three prospective studies
- **Patient population**:
  - 162 patients (52 pediatric)
- **End points**:
  - Seizure control
  - Clinical outcomes and adverse effects

**NMDA Antagonists for RSE - Review**

- **Ketamine doses used**
  - Adults: Bolus max 5 mg/kg; CI 0.12-10 mg/kg/hr
  - Pediatrics: Bolus max 3 mg/kg; CI max 10 mg/kg/hr
- **Time to administration of ketamine**
  - Five hours to 140 days
- **Number of AEDs prior to ketamine introduction**
  - One to eleven
- **Ketamine treatment duration**
  - Two hours to 27 days

**NMDA Antagonists for RSE - Review**

- **Results**
  - Adults
    - Complete response – 59 patients (53.6%)
    - Treatment failure – 51 (46.4%)
  - Pediatrics
    - Complete response – 33 patients (63.5%)
    - Treatment failure – 19 patients (36.5%)
- **Adverse effects**
  - Two patients – cardiac arrhythmias

**NMDA Antagonists for RSE – Conclusions**

- Efficacy of ketamine promising
- Response rate was highest when ketamine was introduced “early”
- Response was not likely if ketamine was introduced after seven days of RSE
- Poor clinical outcomes associated with late administration
- Comparable efficacy with guideline recommended anesthetics

**Pharmacists’ Role**

- To be familiar with recent guidelines and current institutional practice
- Make appropriate and timely recommendations in regards to pharmacotherapy
- Stay tune for further research on role of ketamine in treatment of RSE
Summary

• Defined SE and RSE
• Reviewed etiology and pathophysiology
• Analyzed the role of the emerging treatment for RSE, ketamine
• Explained important role of pharmacists for successful treatment of RSE

References


Controversial Role of Ketamine in Treatment of Refractory Status Epilepticus

Senka Runjaic, PharmD
PGY-1 Pharmacy Resident
January 24, 2015