KETAMINE FOR EXCITED DELIRIUM SYNDROME

Gary Andolfatto

Attending Physician and ED Research Director, Lions Gate Hospital

Assistant Professor, UBC Dept of Emergency Medicine
Objectives

• Describe the Excited Delirium Syndrome

• Discuss the use of ketamine for control of Excited Delirium

• Discuss practical use considerations and possible complications
Disclosure

No financial interests to disclose
What is “Excited Delirium Syndrome”? 

ExDS

More than just agitation
ExDS - Definition

• “A syndrome of uncertain etiology characterized by delirium, agitation, and hyperadrenergic autonomic dysfunction.”

(American College of Emergency Physicians Task Force 2009)
ExDS - Definition

- “A syndrome of uncertain etiology characterized by delirium, agitation, and hyperadrenergic autonomic dysfunction.”
- American College of Emergency Physicians Task force 2009

- **Delirium**: a state of mental confusion fluctuating in intensity manifested by:
  - Disorientation, incoherence, memory disturbance
  - Hallucinations, delusions,
ExDS - Definition

• “A state of extreme mental and physiological excitement, characterized by extreme agitation, hyperthermia, hostility, exceptional strength, and endurance without apparent fatigue.”

• - Morrison 2001
ExDS – Who gets it?

- Usually male
- Mean age mid-late 30’s
- Sudden onset
- Often history of mental illness
- VERY often history of psycho-stimulant abuse
ExDS – What does it look like?

- Unable to concentrate
- Extremely restless
- Cannot remain still
- Flailing
- Diaphoretic
- Flushed skin
- Extreme tachycardia
- Shedding clothes
- Attraction to glass / mirrors
ExDS - What causes it?
ExDS - What causes it?

- No one really knows

- Associated with:
  - Stimulant drug use, especially cocaine
  - Psychiatric disease / drug withdrawal
  - Metabolic disorders / genetic susceptibility?

- Post mortem studies have suggested excessive dopamine stimulation in the striatum of the brain

- This may also explain disordered thermoregulation
In Simple Terms.

- Sympathetic nervous system over-activation
- Fight or Flight response
- Put your car in park and push the gas pedal to the floor
- How long till the engine blows up?
Typical sequence of events

- 911 call – man running down the street naked
- Struggle ensues with multiple officers
- Necessity to use baton, choke holds, tazer, “swarm technique”
- Physical restraints applied
- Noticed to be unresponsive
- Local media headlines ensue
What happened?

- Hyper-stimulation
- Hyperthermia
- Severe acidosis
- Rhabdomyolysis

- Acidosis leads to brady-asystolic arrest

- Majority of deaths occur after violent struggle
  - some hypoxia the final straw??
Goals of Medical Therapy

- Stabilize the underlying medical processes
Goals of Medical Therapy

• FIRST MUST CONTROL BEHAVIOR
Drugs used for sedation in ExDS

- **Benzodiazepines**
  - Midazolam / lorazepam
  - IV/IM/IN
  - Onset 5-15 min; duration 30-60 min

- **Antipsychotics**
  - Haldol / Droperidol
  - IV / IM
  - Onset 15-20 min; duration 3-6 hours

- **Atypical antipsychotics**
  - Olanzapine
  - PO / IM
  - Onset 15-30 min; duration 24 hours
Problems with these options

• Most are more effective by IV route
  • - can you see a problem?

• Midazolam effective by IM – but respiratory depression as high doses are usually required

• Antipsychotics have slow onset of effect
The ideal agent

- Single dose
- Can give IM
- Immediate effect
- No effect on respiratory function
- No negative hemodynamic effects
That sounds a lot like ........
A short history of ketamine …

• Invented in 1962

• 1966: Patented by Parke-Davis and used in Vietnam War – attempting to find a safer anesthetic alternative

• 1970: FDA approval for use in children and elderly

• 1981: Controlled substance status; concerns regarding psychotropic effects; ICP effects fell out of favour for medical use
The resurgence of ketamine

- Most used anesthetic agent world-wide
  - 172 developing world physicians reported 1 serious adverse event in 12,800 administrations with NO monitoring

- Classic for pediatric procedural sedation

- ICP concerns now de-bunked

- COMMONLY used in the ED
  - Procedural sedation
  - IV infusion for pain
  - IN administration for pain – ED / pre-hospital / ?WRs

Soon to be used for depression / suicidality?!
How does Ketamine work?

- Blocks NMDA receptor → depresses the sensory association areas of the cortex as well as the limbic system.

- The limbic system integrates peripheral sensory signals and involved in memory development

→ Thus ketamine results in the inability to process peripheral pain signals or form memory

→ patient becomes completely unaware of the outside world (at high doses);
Ketamine dosing (IV)

- **The analgesia zone: 0.1 – 0.3 mg/kg**
  - No effect on perception or emotion
  - Good analgesia
  - No monitoring required

- **The recreational zone: 0.3 – 0.6 mg/kg**
  - Good analgesia, but high

- **The partially dissociated zone: 0.5 – 0.8 mg/kg**
  - Some awareness but altered response
  - Can be frightening

- **Full dissociation: >0.8 mg/kg / 4-5 mg/kg IM**
  - “Right f@cking out of it, man … “
Ketamine dosing (IV)

- The analgesia zone: 0.1 – 0.3 mg/kg
  - No effect on perception or emotion
  - Good analgesia

DOSE RESPONSE IS VARIABLE IN THE MID-RANGES

- Full dissociation: >0.8 mg/kg / 4-5 mg/kg IM
  - “Right f@cking out of it, man … “

The “Dissociation Threshold” concept – more is not more!
Ketamine is attractive for ExDS

- You can’t provide medical care until you restrain the patient
- You can’t restrain the patient until you provide sedation
- Most other agents are too slow or require an IV
Is IM ketamine the *ideal* agent?

- RAPID CONTROL - onset IM 1-2 minutes
- Give right through clothing
- 5 mg/kg provides dissociation for 20 – 30 minutes
- **CAREGIVER SAFETY!**
  - NO respiratory depression
  - NO hypotension (inhibits catecholamine re-uptake)
  - High minute ventilation buffers acidosis
  - **PATIENT SAFETY!**

- This allows soft restraints / transport / work-up / treatment to commence
Hang on there … what about bad stuff that can happen with ketamine?

- Ketamine concerns:
  - 1) Laryngospasm
  - 2) Hypersalivation
  - 3) Vomiting
  - 4) Possible drug interactions
  - 5) Hypertension
  - 6) Cardiac stimulation
From the sedation literature:

- Ketamine concerns:
  - 1) Laryngospasm: 0.3% (22 cases in 8,283 pts)
  - 2) Hypersalivation: 0.1% (1 case in 950 pts)
  - 3) Vomiting: 10% - after recovery (5% with ondansetron)
  - 4) Possible drug interactions: No evidence
  - 5) Hypertension: Common in normals – transient, no tx
  - 6) Cardiac stimulation: No evidence of harm; used in cardiac surgery often
VERY rare stuff

- That everyone (who is a keta-geek) likes to talk about……

**APNEA:**

Can be rarely seen with rapid IV push
Transient

**EXTREME RIGIDITY**

Somewhere around 1:10,000 occurrence
Can be scary if it happens!
Difficult to differentiate from seizure

**SEIZURE**

Ketamine is a known anti-epileptic – in NORMAL brains
Possibly reduces seizure threshold in abnormal brains
What’s the evidence for use of ketamine in Excited Delirium Syndrome?
The combative multitrauma patient: a protocol for prehospital management
Eitan Melamed, Yahav Oron, Ron Ben-Avraham, Amir Blumenfeld and Guy Lin

European J of Emergency Medicine. 2007;14:265-68
Retrospective pre-hospital case series of 11 patients - 2-yr period

Combative trauma patients

Protocol using 5 mg/kg IM ketamine – half got midazolam 5 mg IM

Authors felt that pre-hospital intubation avoided in many cases

No adverse effects attributable to ketamine
50 of 52 cases had good sedation (Ketamine 4mg/kg IM)

3 cases of respiratory depression
   1 treated with BVM
   2 intubated

All 3 of these cases had received midazolam
51 patient case series – retrospective analysis
Mean dose of 5 mg/kg IM ketamine.
29% of patients were intubated in the ED – most commonly for airway protection (for imaging)
Only one was hypoxic -- 60% were alcohol intoxicated.

Higher doses of ketamine lead to higher chance of intubation in hospital
Similar to intubation rate seen with Droperidol. Lower rate of intubation compared to midazolam.
Analysis

- ExDS is a tough situation that is tough to study – real evidence is small in numbers and preliminary.

- No rigorous studies showing advantage of one approach over another.

- Lots of experience with IM ketamine that seems to support it as a good, maybe even the best option.

- Good theoretical reasons to use ketamine and very positive small initial reports
What might I expect when Jack is NOT being a dull-boy?
Jack

- 100 kg

- Wide-eyed; Sweating; Wild and swinging

- Brought in (barely) by 5 police officers

- Doc says: “Get me some ketamine .. NOW (please…)”
• Dose = 5mg / kg

→ 500mg IM ketamine

→ Ketamine is 50mg/ml = 10ml

→ Get 4 syringes of 2.5 ml each (or more!)

→ One into each beefy limb (this is a team sport)
→ or 2 into each thigh

→ Expect a big pussy-cat in about 2 minutes
What then?

- Quickly apply 4-pt restraints and apply monitors
- Get vitals / glucometer
- Get labs and IV / IO access
- Expect the bear to start stirring in 20 – 30 minutes
- Prepare for longer-term chemical restraint
- Fluid resuscitation / cooling
Treatment of ExDS

Excited Delirium Syndrome

- Agitation
- Acidosis
- Hyperthermia

“Treat the Triad!”

Treatment Triad
Don’t forget the causes

<table>
<thead>
<tr>
<th>Letter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Alcohol</td>
</tr>
<tr>
<td>E</td>
<td>Endocrine, Encephalopathy, Electrolytes</td>
</tr>
<tr>
<td>I</td>
<td>Insulin (hypoglycemia)</td>
</tr>
<tr>
<td>O</td>
<td>Oxygen (hypoxia), Opiates (drugs of abuse)</td>
</tr>
<tr>
<td>U</td>
<td>Uremia</td>
</tr>
<tr>
<td>T</td>
<td>Toxins, Trauma, Temperature</td>
</tr>
<tr>
<td>I</td>
<td>Infection</td>
</tr>
<tr>
<td>P</td>
<td>Psychiatric, Porphyria</td>
</tr>
<tr>
<td>S</td>
<td>Stroke, Shock, Subarachnoid Hemorrhage, Space-Occupying CNS Lesion</td>
</tr>
</tbody>
</table>
Things that can go wrong

- *Jack doesn’t become a pussy cat:*
Things that can go wrong

- Jack doesn’t become a pussy cat:
- UNDER-dosing is the likeliest problem
- **GO BIG**
- 4 mg/kg IM is MINIMUM
- Better to aim high
- Good literature for 5mg/kg IM in sedation
- Remember the DISSOCIATION THRESHOLD concept
Things that can go wrong

- Jack was asleep – now he’s REALLY screaming as he’s waking up ….
Things that can go wrong

• Jack was asleep – now he’s REALLY screaming as he’s waking up ….

• The big dose put him in the dissociation zone
• Now his levels are falling and he’s going thru “partial dissociation”
• Solution?
• Give him more ketamine again and deal with it later
• Give him midazolam and talk nice!
Things that can go wrong

- Jack stops breathing:

- Probably NOT the ketamine (unless you gave it all IV)

- Usual intervention – BVM / intubate
Things that can go wrong

- Jack gets stridor and occludes his airway
- Nasty luck! Laryngospasm!
- He can be BAGGED
- Can’t bag??
- Paralyze and intubate
- Change your underwear later
Things that can go wrong

• Jack stiffens up – totally rigid:

• OK as long as breathing and saturating

• If not – BVM

• Can’t BVM?
• Paralyze and intubate
• Publish the case report b/c it’s so damn rare!
Conclusions

- These are tough patients who are sick for a variety of reasons
- Expect trouble!
- *Ketamine is most likely to get you OUT of trouble – much much less likely to cause trouble.*
- Don’t under-dose!
- Remember to treat the triad
- Stay tuned for more experience and more literature to be published – especially pre-hospital
gandolfatto@gmail.com

- Questions?
- Relationship advice?