Nosocomial Injection:
Intranasal Midazolam for Pediatric Seizures

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DISCLOSURE

- Dr. Keseg has no financial interest in any companies that are involved in the manufacture of products related to this presentation.
# CFD EMS Overview

## Geographical Information

<table>
<thead>
<tr>
<th>Area</th>
<th>Size</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metro Columbus</td>
<td>399.1 square miles</td>
<td>1,742,798</td>
</tr>
<tr>
<td>City of Columbus</td>
<td>239.9 square miles</td>
<td>791,868</td>
</tr>
</tbody>
</table>
First Line Apparatus Summary

Emergency Units in Service

- 34 Engines
- 15 Ladders
- 5 Rescues
- 7 Battalion Chiefs
- 32 Medics
- 1 HazMat
- 7 EMS Supervisors
- 1 Air Supply
- 1 Bomb Squad
- 1 Safety Officer
- 11 Boats
CFD EMS OVERVIEW

• All ALS Fire based EMS System
• Two EMT-Ps on each Medic Vehicle (32)
• At least one EMT-P on each engine (34)
• Engine/medic stations
• Seven EMS Officers

FOUR-YEAR COMPARISONS

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Incidents</td>
<td>146,144</td>
<td>142,981</td>
<td>148,918</td>
<td>161,693</td>
</tr>
<tr>
<td>Fire Incidents</td>
<td>24,868</td>
<td>21,470</td>
<td>21,861</td>
<td>23,715</td>
</tr>
<tr>
<td>EMS Incidents</td>
<td>110,739</td>
<td>110,398</td>
<td>115,311</td>
<td>137,442</td>
</tr>
</tbody>
</table>
Do you know Columbus???

- What was the name of the vehicle that the Columbus Fire Department deployed in 1969 to take care of cardiac patients?
Do you know Columbus???

- THE HEARTMOBILE
IN Midazolam for seizure control

- 150,000 cases of status epilepticus annually
- Morbidity and mortality are at least partially dependent on the duration of seizure activity
- HYPOTHESIS
  - *Intranasal delivery of Midazolam provides a very effective, safe and inexpensive means to rapidly achieve seizure control.*
Why Intranasal?
Which would YOU prefer?
Why Intranasal?

The nose is a preferred access point for medication administration because:

• *Training is minimal*

• *No shots are needed*

• *It is virtually painless*

• *It eliminates any risk of a needle stick*
Nasal Mucosa

- The rich vascular plexus of the nasal cavity provides a direct route into the bloodstream for medications that easily cross mucous membranes.
Nasal Mucosa

- The total surface area available in the nasal mucosa is estimated to be about 28 square inches.
Why Intranasal?

IV vs IN serum drug levels - theoretical example of an opiate

- IV medication levels above respiratory depression threshold
- Respiratory depression threshold
- IV medicine therapeutic
- IN medication achieves therapeutic threshold
- Therapeutic efficacy threshold

Serum concentration (Log)

Minutes from delivery
Comparison of CSF/plasma ratios for IN, SL and SC apomorphine

INTRANASAL SUPERIOR TO SUBLINGAL AND SUBCUTANEOUS
<table>
<thead>
<tr>
<th>Key Features</th>
<th>Nasal</th>
<th>Oral</th>
<th>I.V.</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Serum Drug Levels</td>
<td>✔</td>
<td>NO</td>
<td>✔</td>
</tr>
<tr>
<td>Rapid Onset</td>
<td>✔</td>
<td>NO</td>
<td>✔</td>
</tr>
<tr>
<td>Titratable</td>
<td>✔</td>
<td>NO</td>
<td>✔</td>
</tr>
<tr>
<td>Painless</td>
<td>✔</td>
<td>✔</td>
<td>NO</td>
</tr>
<tr>
<td>Easy to Use</td>
<td>✔</td>
<td>✔</td>
<td>NO</td>
</tr>
<tr>
<td>Low Resource Utilization</td>
<td>✔</td>
<td>✔</td>
<td>NO</td>
</tr>
</tbody>
</table>
How to give drugs intranasally

- Fragment the medication into fine particles so:
  - *maximal* nasal mucosal surface is covered and
  - *minimal* volume runs out the nose or into the throat
Mucosal Atomization Device
MAD device

- Device designed to allow emergency personnel to delivery nasal medications as an atomized spray.
  - Broad 30-micron spray ensure excellent mucosal coverage.
- Cost: $3.32 apiece
  - Translation: CHEAP!!!!
How To Use the Nasal Device

Remove and discard the green vial adapter cap.
Pierce the medication vial with the syringe vial adapter.
Aspirate the proper volume of medication required to treat the patient (an extra 0.1ml of medication should be drawn up to account for the dead space in the device).
Remove (twist off) the syringe from the vial adapter.

BOTTOM LINE: IT’S EASY!!!!!!
Tips on IN Administration

- Utilize both nostrils
Tips on IN Administration

- Be knowledgeable of the “dead space” within the MAD
Tips on IN Administration

Minimize volume,

- 1/3 mL per nostril is ideal, 1 mL is maximum

Maximize concentration

- Use the appropriately concentrated drug
Tips on IN Administration

Beware of abnormal mucosal characteristics

- Mucous, blood and vasoconstrictors reduce absorption
- Suction nostrils or consider alternate drug delivery method in these situations
Nasal Drug Delivery in EMS: What Medications?

- Drugs of interest to EMS systems:
  - Intranasal naloxone (Naloxone)
  - Intranasal midazolam (Midazolam)
  - Intranasal Fentanyl
  - Intranasal Glucagon
  - Intranasal Ketamine
  - Intranasal Epinephrine
  - Others
EAGLES Experience

- 30 responses
  - 25 using IN
    - 3 soon
  - 24 using Naloxone
  - 18 using midazolam
  - 11 using fentanyl
  - 3 using glucagon
  - 1 dilaudid
  - 1 influenza vaccine
SUMMARY
Intranasal Midazolam: advantages in EMS seizure treatment

- No needles
- Rapid delivery
- Training is easy
- Socially acceptable
But does intranasal Midazolam work in Pediatric seizures?
Intranasal Midazolam Research Studies

- Seizures.
    - Prospective study: **IN midazolam** versus **IV diazepam** for prolonged seizures (>10 minutes) in children.
    - **Similar efficacy** in stopping seizures (app. 90%).
  - **Time to seizure cessation:**
    - **IV Diazepam:** 8.0 minutes.
    - **IN Midazolam:** 6.1 minutes.
IN Midazolam is preferable to rectal diazepam in the treatment of seizures in children. It’s administration is easy, it has a rapid onset of action, has no significant effect on respiration and oxygen saturation and is socially acceptable.
Intranasal Midazolam can possibly be used not only in medical centers but also in general practice and at home after appropriate instructions are given to families of children with recurrent seizures.
Intranasal Midazolam vs Rectal Diazepam for the Home Treatment of Acute Seizures in Pediatric Patients With Epilepsy

Maija Holsti, MD, MPH; Nanette Dudley, MD; Jeff Schunk, MD; Kathleen Adelgais, MD, MPH; Richard Greenberg, MD; Cody Olsen, MS; Aaron Healy, BS; Sean Firth, PhD, MPH; Francis Filloux, MD

We found no detectable difference in efficacy between IN-MMAD and RD as a rescue medication. However, our data suggest that there may be a trend toward faster seizure control in the IN-MMAD group. The published literature in the ED setting also suggests that IN midazolam may stop seizures more quickly than RD. Adverse effects appear to be minimal. Given the ease of administration/overall satisfaction, IN-MMAD may be considered an alternative to rectal diazepam as a rescue medication for the in-home treatment of prolonged seizures in children.
Intranasal Midazolam

MORE Research Studies

• Rectal diazepam fails to abort about 40 percent of seizures in randomized controlled trials.

• Several randomized trials now demonstrate that transmucosal intranasal midazolam is as effective as intravenous diazepam and more effective than rectal diazepam in aborting prolonged seizures.
  - (J Child Neurol 2002;17:123; Brit Med J 2000;321:83; Epilepsy Behav 2004;5:253.)

• In addition, its preference over rectal diazepam by caregivers and its safety as home therapy have been established in multiple small studies.
BOTTOM LINE:

**IN** Midazolam as good and probably better than PR Diazepam in pediatric seizures
CFD Implementation of IN Midazolam

- Analysis of product: Jan-May 2003
- Recommendations Nasal Device: June 2003
- Training/Protocol development: Oct 2003
- Training completed: December 2003
- Devices deployed: Feb 2004
CFD Protocol for IN Midazolam

- For treatment of persistent seizure activity

Procedure:
- Assess ABC’s – Airway, Breathing, Circulation
- For pulseless patients, proceed to ACLS guidelines
- Apply 100% oxygen NRB mask to seizing patient
- Use age based table to determine proper volume of Midazolam for atomization:
<table>
<thead>
<tr>
<th>Patient age (years)</th>
<th>Weight (kg)</th>
<th>IN Versed volume in ml* 5mg/ml concentration</th>
<th>IN volume (ml)</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>3 kg</td>
<td>IN volume (ml)</td>
<td>0.3 ml</td>
<td>0.6 mg</td>
</tr>
<tr>
<td>&lt;1 yr</td>
<td>6 kg</td>
<td>IN volume (ml)</td>
<td>0.4 ml</td>
<td>1.2 mg</td>
</tr>
<tr>
<td>1 yr</td>
<td>10 kg</td>
<td>IN volume (ml)</td>
<td>0.5 ml</td>
<td>2.0 mg</td>
</tr>
<tr>
<td>2 yr</td>
<td>14 kg</td>
<td>IN volume (ml)</td>
<td>0.7 ml</td>
<td>2.8 mg</td>
</tr>
<tr>
<td>3 yr</td>
<td>16 kg</td>
<td>IN volume (ml)</td>
<td>0.8 ml</td>
<td>3.2 mg</td>
</tr>
<tr>
<td>4 yr</td>
<td>18 kg</td>
<td>IN volume (ml)</td>
<td>0.9 ml</td>
<td>3.6 mg</td>
</tr>
<tr>
<td>5 yr</td>
<td>20 kg</td>
<td>IN volume (ml)</td>
<td>1.0 ml</td>
<td>4.0 mg</td>
</tr>
<tr>
<td>6 yr</td>
<td>22 kg</td>
<td>IN volume (ml)</td>
<td>1.0 ml</td>
<td>4.4 mg</td>
</tr>
<tr>
<td>7 yr</td>
<td>24 kg</td>
<td>IN volume (ml)</td>
<td>1.1 ml</td>
<td>4.8 mg</td>
</tr>
<tr>
<td>8 yr</td>
<td>26 kg</td>
<td>IN volume (ml)</td>
<td>1.2 ml</td>
<td>5.2 mg</td>
</tr>
<tr>
<td>9 yr</td>
<td>28 kg</td>
<td>IN volume (ml)</td>
<td>1.3 ml</td>
<td>5.6 mg</td>
</tr>
<tr>
<td>10 yr</td>
<td>30 kg</td>
<td>IN volume (ml)</td>
<td>1.4 ml</td>
<td>6.0 mg</td>
</tr>
<tr>
<td>11 yr</td>
<td>32 kg</td>
<td>IN volume (ml)</td>
<td>1.4 ml</td>
<td>6.4 mg</td>
</tr>
<tr>
<td>12 yr</td>
<td>34 kg</td>
<td>IN volume (ml)</td>
<td>1.5 ml</td>
<td>6.8 mg</td>
</tr>
<tr>
<td>Small teenager</td>
<td>40 kg</td>
<td>IN volume (ml)</td>
<td>1.8 ml</td>
<td>8.0 mg</td>
</tr>
<tr>
<td>Adult or full-grown teenager</td>
<td>≤ 50 kg</td>
<td>IN volume (ml)</td>
<td>2.0 ml</td>
<td>10.0 mg</td>
</tr>
</tbody>
</table>
Survey on IN Midazolam use

- Distributed to all EMS personnel on medics:
  - IN Midazolam used most often for seizures (81%)
  - IN Midazolam used 0 - 5 times per month (97%)
  - 96% felt comfortable administering IN Midazolam
  - 93% felt it somewhat or greatly enhanced their practice
### Pediatric seizure patients given Intranasal Midazolam

<table>
<thead>
<tr>
<th>Year</th>
<th>Number treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>10</td>
</tr>
<tr>
<td>2009</td>
<td>21</td>
</tr>
<tr>
<td>2010</td>
<td>21</td>
</tr>
<tr>
<td>2011</td>
<td>25</td>
</tr>
<tr>
<td>2012</td>
<td>14 (as of 8/2012)</td>
</tr>
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</table>
### Conversion Rate of pediatric seizure patients given Intranasal Midazolam

<table>
<thead>
<tr>
<th>Year</th>
<th>Conversion Rate</th>
</tr>
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<tbody>
<tr>
<td>2008</td>
<td>50%</td>
</tr>
<tr>
<td>2009</td>
<td>80%</td>
</tr>
<tr>
<td>2010</td>
<td>64%</td>
</tr>
<tr>
<td>2011</td>
<td>75%</td>
</tr>
<tr>
<td>2012</td>
<td>72% (as of 8/2012)</td>
</tr>
</tbody>
</table>
Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus

Robert Silbergleit, M.D., Valerie Durkalski, Ph.D., Daniel Lowenstein, M.D., Robin Conwit, M.D., Arthur Pacioli, M.D., Yuko Palesch, Ph.D., and William Barsan, M.D., for the NETT Investigators*

CONCLUSIONS
For subjects in status epilepticus, intramuscular midazolam is at least as safe and effective as intravenous lorazepam for prehospital seizure cessation. (Funded by the National Institute of Neurological Disorders and Stroke and others; ClinicalTrials.gov number, NCT00809146.)

NO HEAD TO HEAD COMPARISON WITH INTRANASAL MIDAZOLAM
IN Midazolam for seizure control

IN MIDAZOLAM MUCH MORE RAPID ONSET THAN IM
Take away lessons for nasal midazolam:

- **Dose and volume:**
  - Higher concentration: 5mg/ml IV solution.
- **Dosing calculations can be difficult:**
  - Use a predefined weight based table
- **Deliver immediately on decision to treat:**
  - Atomize into nose with MAD, then begin standard care.
- **Efficacy:**
  - Not quite 100% effective so failures with nasal may need follow-up with IV therapy.
NASAL MIDAZOLAM IS AN EFFECTIVE EMS TREATMENT FOR PEDIATRIC SEIZURES
Questions???????????