Intranasal Drug Delivery
An Alternative in Select Cases

- Active research
- Painless, needleless, non-invasive
- No sterile technique
- Immediately available
- Extensive absorptive surface/good blood flow
- Rapid drug absorption into blood and CSF

Outline:
1. Intranasal drug delivery
   - Naloxone
2. Hydrofluoric acid burns
   - Topical calcium therapy
3. Chemical nerve agent exposure
   - Rapid atropine synthesis

Intranasal Drug Delivery

- Desirable properties
  - Low M.W.
  - High potency
  - Water soluble
  - Lipophilic
  - Less than 1 mL
- Sufentanil, fentanyl
  - Pain control, sedation
- Midazolam
  - Sedation, seizures
- Ketamine
  - Sedation
- Lidocaine
  - Nasal procedures
- Haloperidol
  - Acute psychosis

Naloxone

- Boston: Bystander administered IN
  - 385 participants, 74 successful OD reversals
- Case Series, IN followed by IV
  - 11/30 (37%) patients responded to naloxone
  - 10/11 (91%) responded to IN alone
  - 4/11 (36%) required IV dose
- Prospective non-randomized, IN followed by IV
  - 52/95 (55%) responded to naloxone
    - 43/52 (83%) responded to IN alone
    - 7/52 (13%) required IV dose

References:
IN Naloxone Delivery is an Alternative to IV Therapy For Opioid Overdose

- Retrospective, non-randomized pre-hospital study
- Inclusion: 277 patients who received naloxone by paramedics between Jan 1, 2005 – Dec 31, 2007

<table>
<thead>
<tr>
<th>Opioid Exposure</th>
<th>IV</th>
<th>IN</th>
<th>IM</th>
<th>IO</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed</td>
<td>55</td>
<td>38</td>
<td>3</td>
<td>0</td>
<td>96</td>
</tr>
<tr>
<td>Unknown</td>
<td>148</td>
<td>28</td>
<td>4</td>
<td>1</td>
<td>181</td>
</tr>
<tr>
<td>Total</td>
<td>203</td>
<td>66</td>
<td>7</td>
<td>1</td>
<td>277</td>
</tr>
</tbody>
</table>


Results: Confirmed Overdoses

<table>
<thead>
<tr>
<th></th>
<th>IV (N=55)</th>
<th>IN (N=38)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial RR (BPM)</td>
<td>10.47</td>
<td>9.68</td>
<td>0.60</td>
</tr>
<tr>
<td>Initial GCS</td>
<td>7.00</td>
<td>6.03</td>
<td>0.38</td>
</tr>
<tr>
<td>Final RR (BPM)</td>
<td>17.65</td>
<td>14.05</td>
<td>0.001*</td>
</tr>
<tr>
<td>Final GCS</td>
<td>12.44</td>
<td>10.32</td>
<td>0.05*</td>
</tr>
<tr>
<td>Change in RR (BPM)</td>
<td>7.18</td>
<td>4.37</td>
<td>0.08</td>
</tr>
<tr>
<td>Change in GCS</td>
<td>5.44</td>
<td>4.29</td>
<td>0.19</td>
</tr>
</tbody>
</table>


Discussions/Conclusions

- IV vs. IN: Improvement in GCS and RR which was not significantly different.
- Clinical significance
- IN is a viable alternative to IV
- Prevention of needle stick injury in chaotic pre-hospital setting

Hydrofluoric Acid

- Usage
  - Industrial: Plastic production, metal cleaning, electronics, glass etching
  - Household: Rust removal, aluminum brighteners, heavy duty cleaners
- Tissue damage
  - Hydrogen ion: superficial burn
  - Fluoride ion: penetrating liquefaction necrosis
- Untreated burns
  - Increase in area and depth for days to weeks

Patient Case

- 42 year old female presents complaining of a throbbing painful right index finger. She used a rust removal product for some stains in her bath tub about 24 hours ago. She wore gloves but was unaware that the finger of the glove had ripped.
- Physical exam: pale blanched area with surrounding erythema
- She brought the product to the E.D. its contents included hydrofluoric acid 25%

Hydrofluoric Acid Burn: Treatment

- Copious irrigation for 30 minutes
- Calcium treatment
  - Topical therapy
  - Local infiltrative therapy
  - IV and intra-arterial administration
Topical Calcium Therapy
Extemporaneous Preparation
- Ca Gluconate powder: 3.5 gm to 5 ounce water soluble surgical lubricant (K-Y Jelly®, Surgilube®)
- Use Ca Gluconate 10% 35 mL
- Calcium Carbonate tablets: Triturating Ten 10 gm tablets into a powder and add to 20 ml of water soluble lubricant gel (K-Y Jelly®, Surgilube®) to produce a 32.5% slurry
- Corn starch, methyl cellulose, other inert thickeners
- Added to produce a more spreadable gel
- Redress burns at least every 4 hours

Chemical Weapons: Nerve Agents
Nerve Agent Tabun GA Sarin GB Soman GD VX VX
- Mechanism: Cholinesterase inhibitors, excessive buildup of acetylcholine (Ach)

Nerve Agents
- Muscarinic effects
  - Postganglionic parasympathetic
- Nicotinic effects
  - Preganglionic sympathetic & parasympathetic
  - Neuromuscular junction
  - Excess Ach in CNS

Results of Cholinesterase Inhibition
- Muscarinic
  - Diarrhea Derivation Miosis* Salivation Urination Urination
  - Bronchospasm GI symptoms Emesis
  - Emesis
  - CNS
  - Anxiety, confusion, ataxia, dysarthria, coma, seizures*, respiratory depression*

* Most important after nerve agents

Treatment
- Selective protective measures
- Irrigation
  - Water, hypochlorite solution, alkaline soap
- Atropine
- Pralidoxime (Protopam*) (2-PAM)

Atropine
- Competitive MUSCARINIC antagonist
  - Peripheral > central
  - Dosing (IV or IM)
    - Initial: Adult 2mg
    - Peds 0.02 mg/kg (min 0.1mg)
    - Repeat every 2-3 minutes
    - May require 2-3 times this initial dose in mod to severe cases
  - Endpoint
    - Reversal of Muscarinic effects

- Dosing in comparison to organic phosphorus insecticides
- Tokyo subway sarin attacks (N=111)*
  - Doses > 2 mg 18.9%
  - Max dose 9 mg
  - Adverse effects
    - Dry mouth & skin, mydriasis, paralysis of accommodation, tachycardia

### Atropine: Alternative Routes and Supply Sources

- Aerosolized
- Ophthalmic
- Miosis reversal
- Causes photophobia and loss of accommodation
- Glycopyrrolate
- IV administration of:
  - EMS sources
  - Ophthalmic
  - Veterinary
  - Powder preparation

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### Rapid Atropine Reformulation From Bulk Powder

1. Empty contents of the atropine 0.1 mg/ml (10 ml syringes) into 500 ml bottle. Total volume should be 330 ml with the overfill
2. Open 500 ml bottle with pliers while maintaining sterility of rubber stopper
3. Add 627 mg of atropine powder, reclose bottle, and shake well until clear
4. Filter into the second 500 ml bottle with 0.22 um filter
5. Use syringe pump to fill 100 (3 ml) syringes with 3ml of atropine and label syringes

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### Rapid Atropine Synthesis for Treating Massive Nerve Agent Exposure

<table>
<thead>
<tr>
<th>Item Needed</th>
<th>Quantity</th>
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<tbody>
<tr>
<td>Scale</td>
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</tr>
<tr>
<td>Atropine powder</td>
<td>2 gms</td>
</tr>
<tr>
<td>Sterile Water 50 ml</td>
<td>1 vial</td>
</tr>
<tr>
<td>Filter and 18-gauge needle for transfer</td>
<td>1</td>
</tr>
<tr>
<td>Normal Saline 1000 ml</td>
<td>1</td>
</tr>
<tr>
<td>3 ml syringes</td>
<td>100</td>
</tr>
<tr>
<td>Syringe batch system and 60ml syringe</td>
<td>1</td>
</tr>
<tr>
<td>Labels</td>
<td>100</td>
</tr>
<tr>
<td>Alcohol swabs</td>
<td></td>
</tr>
</tbody>
</table>

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### Rapid Atropine Synthesis for Treating Massive Nerve Agent Exposure

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Time (min)</th>
<th>Cumulative Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Weigh out atropine</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>2. Dilute in 10 ml sterile water</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3. Prepare NS solution by removing 50 ml</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>4. Instill atropine concentrate using 0.2 um filter</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>5. Print labels</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>6. Connect NS solution to syringe batch system</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>7. Program-calibrate syringe pump</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>8. Compound and label syringes</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>8a. Attach 2-way connector with 60 ml syringe, set up for hand fill</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>8b. Draw up 3ml syringes by hand and label</td>
<td>24</td>
<td>34</td>
</tr>
</tbody>
</table>

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Rapid Atropine Synthesis for Treating Massive Nerve Agent Exposure

- Microbiology testing
- Negative growth at 3 weeks
- Stability testing
- Met USP standards ± 5% at 3 weeks
- Cost
  - $11 vs. $5,000 for equivalent 1mg/10ml syringes


Summary/Conclusion

- Antidote therapy requires timely administration
- Novel approaches are at times necessary
- Pharmacists looked upon for knowledge of preparation and administration
- Rapid responses to patient care necessary
- Education and preplanning by pharmacists can improve patient outcome